

1-[1-(4-Aminophenethyl)piperidin-4-yl]indoline (140 mg) was dissolved in methylene chloride (2 ml). Under ice cooling, methanesulfonyl chloride (0.12 ml) and triethylamine (0.1 ml) were added to the resultant solution followed by stirring for 45 min. After adding a 10% aqueous solution of potassium carbonate, the reaction solution was extracted with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. After evaporating the solvent, the resulting residue (150 mg) was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) to successively give 1-[1-[4-bis(methylsulfonyl)aminophenethyl]piperidin-4-yl]indoline (50 mg) and 1-[1-(4-

methylsulfonylaminophenethyl)piperidin-4-yl]indoline (35 mg)
each as an oil.

(1) 1-{1-[4-bis(methylsulfonyl)aminophenethyl]piperidin-4-yl}indoline

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.71-1.87(4H, m), 2.09-2.18(2H, m), 2.60-2.66(2H, m), 2.83-2.89(2H, m), 2.95(2H, t, J=8.4Hz), 3.08-3.15(2H, m), 3.35-3.45(3H, m), 3.39(6H, s), 6.41(1H, d, J=7.5Hz), 6.60(1H, t, J=7.5Hz), 7.01-7.07(2H, m), 7.25-7.33(4H, m).

FAB-Mass: 478(MH⁺).

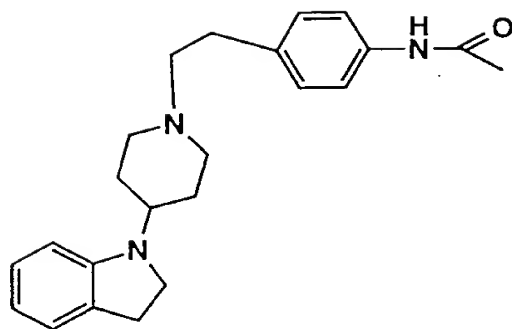
(2) 1-[1-(4-methylsulfonylaminophenethyl)piperidin-4-yl]indoline

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.52-1.66(4H, m), 2.00-2.08(2H, m), 2.64-2.70(2H, m), 2.80-2.86(2H, m), 2.96-3.02(2H, m), 3.25-3.40(3H, m), 3.32(3H, s), 6.41(1H, d, J=7.4Hz), 6.48(1H, t, J=7.4Hz), 6.91-6.99(2H, m), 7.07-7.19(4H, m).

FAB-Mass: 400(MH⁺).

Example 32: Synthesis of 1-[1-(4-acetamidophenethyl)piperidin-4-yl]indoline



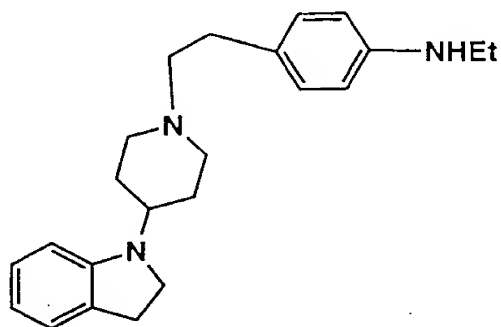
1-[1-(4-Aminophenethyl)piperidin-4-yl]indoline (310 mg) was dissolved in methylene chloride (3 ml). Under ice cooling, acetyl chloride (0.103 ml) was added to the resultant solution followed by stirring the obtained mixture for 45 min. After adding a 10% aqueous solution of potassium carbonate, the reaction solution was extracted with ethyl acetate. Then the organic layer was washed with brine and dried over magnesium sulfate. After evaporating the solvent, the resulting residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (200 mg) as an oil.

$^1\text{H-NMR}$ (400 MHz, CDCl_3):

$\delta(\text{ppm})$ 1.70-1.86(4H, m), 2.08-2.16(2H, m), 2.17(3H, s), 2.56-2.62(2H, m), 2.76-2.82(2H, m), 2.95(2H, t, $J=8.4\text{Hz}$), 3.08-3.14(2H, m), 3.35-3.44(3H, m), 6.41(1H, d, $J=7.5\text{Hz}$), 6.60(1H, t, $J=7.5\text{Hz}$), 7.04(1H, t, $J=7.5\text{Hz}$), 7.10(1H, br-s), 7.16(2H, d, $J=8.4\text{Hz}$), 7.40(2H, d, $J=8.4\text{Hz}$).

FAB-Mass: 364(MH $^+$).

Example 33: Synthesis of 1-[1-(4-ethylaminophenethyl)piperidin-4-yl]indoline



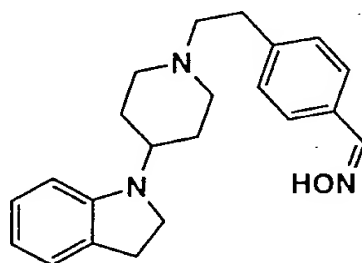
1-[1-(4-Acetaminophenethyl)piperidin-4-yl]indoline (135 mg) was dissolved in tetrahydrofuran (5 ml). After adding lithium aluminum hydride (28 mg) at room temperature, the resultant mixture was heated under reflux for 2 hr. After adding water, the reaction solution was extracted with ethyl acetate. Then the organic layer was washed with brine and dried over magnesium sulfate. After evaporating the solvent, the obtained residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (40 mg) as an oil.

$^1\text{H-NMR}$ (400 MHz, CDCl_3):

δ (ppm) 1.25(3H, t, $J=7.1\text{Hz}$), 1.72-1.86(4H, m), 2.06-2.14(2H, m), 2.54-2.60(2H, m), 2.68-2.76(2H, m), 2.91-2.98(2H, m), 3.09-3.16(3H, m), 3.35-3.44(4H, m), 6.41(1H, d, $J=8.0\text{Hz}$), 6.54-6.70(3H, m), 7.00-7.07(4H, m).

Example 34: Synthesis of 1-[1-(4-

hydroxyiminomethylphenethyl)piperidin-4-ylindoline



4-(2-Bromoethyl)benzaloxime (0.49 g) was treated as in Example 2 to give the title compound (0.480 g) as pale yellow crystals (yield: 70.1%).

Free

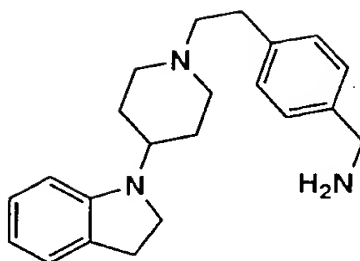
¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.87(4H, m), 2.19(2H, dt, J=3.0, 11.2Hz), 2.68(2H, m), 2.89(2H, m), 2.93(2H, t, J=8.4Hz), 3.20(2H, br-d), 3.40(2H, t, J=8.4Hz), 3.43(1H, m), 6.42(1H, d, J=8.0Hz), 6.61(1H, t, J=8.0Hz), 7.03(1H, t, J=8.0Hz), 7.05(1H, d, J=8.0Hz), 7.21(2H, d, J=8.0Hz), 7.49(2H, d, J=8.0Hz), 8.11(1H, s).

Next, hydrochloric acid was added to the product to give the hygroscopic and amorphous hydrochloride of the title compound was obtained.

FAB-Mass: 350(MH⁺).

Example 35: Synthesis of 1-[1-(4-aminomethylphenethyl)piperidin-4-yl]indoline



1-[1-(4-Hydroxyiminomethylphenethyl)piperidin-4-yl]indoline (2.71 g) was dissolved in tetrahydrofuran (40 ml). Under ice cooling, lithium aluminum hydride (0.59 g) was added thereto and the resultant mixture was heated under reflux for 2 hr. Then the reaction mixture was ice cooled again followed by the addition of water (0.6 ml), a 5 N aqueous solution (0.6 ml) of sodium hydroxide and further water (1.8 ml) thereto. The resulting precipitate was filtered off and the filtrate was washed with ethyl acetate and concentrated under reduced pressure to give the title compound (1.462 g) as a pale yellow oil (yield: 56.2%).

Free

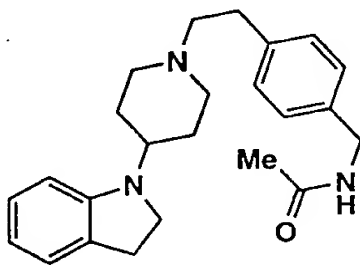
$^1\text{H-NMR}$ (400 MHz, CDCl_3):

$\delta(\text{ppm})$ 1.58(2H, m), 1.79(4H, m), 2.12(2H, dt, $J=3.0$, 11.6Hz), 2.61(2H, m), 2.81(2H, m), 2.95(2H, t, $J=8.4\text{Hz}$), 3.13(2H, br-d), 3.39(2H, t, $J=8.4\text{Hz}$), 3.40(1H, m), 3.84(2H, s), 6.42(1H, d, $J=7.6\text{Hz}$), 6.60(1H, t, $J=7.6\text{Hz}$), 7.04(1H, t, $J=7.6\text{Hz}$), 7.05(1H, d, $J=7.6\text{Hz}$), 7.18(2H, d, $J=8.4\text{Hz}$), 7.24(2H, d, $J=8.4\text{Hz}$).

Next, hydrochloric acid was added to the product to give the hygroscopic and amorphous hydrochloride of the title compound was obtained.

FAB-Mass: 336(MH+).

Example 36: Synthesis of 1-[1-(4-acetamidomethylphenethyl)piperidin-4-yl]indoline



1-[1-(4-Aminomethylphenethyl)piperidin-4-yl]indoline (0.6 g) was dissolved in tetrahydrofuran (9.0 ml). Under ice cooling, acetyl chloride (0.14 ml) was added dropwise thereinto and the resultant mixture was stirred for 2 hr. After adding a saturated aqueous solution of sodium bicarbonate, the mixture was extracted with ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by Cromatorex NH silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (0.518 g) as a pale yellow oil (yield: 79.2%).

Next, hydrochloric acid was added to the product to give the pale yellow, hygroscopic and amorphous hydrochloride of the title compound.

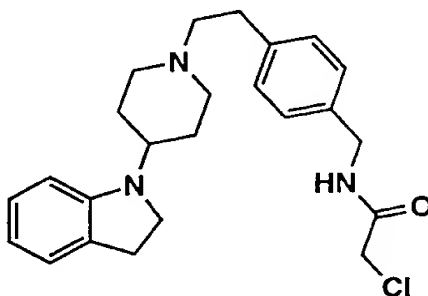
Hydrochloride

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.86(3H, s), 1.90(2H, m), 2.08(2H, m), 2.90(2H, t, J=8.2Hz), 3.08(4H, m), 3.23(2H, m), 3.33(2H, t, J=8.2Hz), 3.63(2H, br-d), 3.74(1H, m), 4.22(2H, d, J=6.0Hz), 6.58(1H, d, J=7.6Hz), 6.59(1H, t, J=7.6Hz), 7.01(1H, t, J=7.6Hz), 7.05(1H, d, J=7.6Hz), 7.23(4H, s), 8.36(1H, t, J=6.0Hz).

FAB-Mass: 378(MH⁺).

Example 37: Synthesis of 1-[1-(4-chloroacetamidomethylphenethyl)piperidin-4-yl]indoline



1-[1-(4-Aminomethylphenethyl)piperidin-4-yl]indoline

(0.1 g) and chloroacetyl chloride (0.026 ml) were treated as in Example 36 to give the title compound (0.074 g) as a pale yellow oil (yield: 62.1%).

Free

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.79(4H, m), 2.12(2H, m), 2.61(2H, m), 2.82(2H, m), 2.94(2H, t, J=8.4Hz), 3.12(2H, br-d), 3.39(2H, t, J=8.4Hz), 3.40(1H, m), 4.13(2H, s), 4.46(2H, d, J=5.6Hz), 6.41(1H, d,

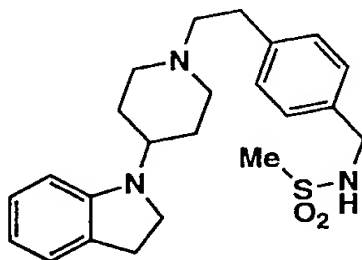
J=7.6Hz), 6.60(1H, t, J=7.6Hz), 6.83(1H, br-s), 7.04(2H, t, J=8.0Hz), 7.20(4H, m).

Next, oxalic acid (8 mg) was added to the above free compound to give a salt followed by recrystallization from a solvent mixture of ethanol with isopropyl ether. Thus, the oxalate (0.054 g) of the title compound was obtained as colorless crystals.

m.p. (oxalate): 138°C.

FAB-Mass: 412(MH+).

Example 38: Synthesis of 1-[1-(4-methanesulfonylaminomethylphenethyl)piperidin-4-yl]indoline



1-[1-(4-Aminomethylphenethyl)piperidin-4-yl]indoline (0.120 g) and methanesulfonyl chloride (0.030 ml) were treated as in Example 36 to give the title compound (0.078 g) as a pale yellow oil (yield: 54.5%).

Free

¹H-NMR (400 MHz, CDCl₃):

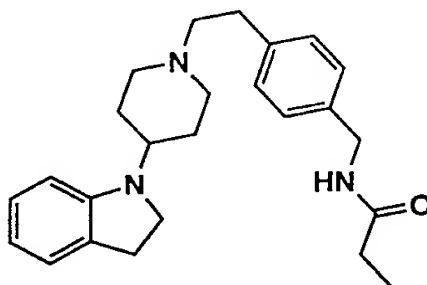
δ(ppm) 1.85(4H, m), 2.20(2H, m), 2.66(2H, m), 2.86(2H, m), 2.89(3H, s), 2.95(2H, t, J=8.7Hz), 3.28(2H, m), 3.39(2H, t, J=8.7Hz), 3.42(1H, m), 4.30(2H, d, J=5.8Hz), 4.63(1H, m),

6.41(1H, d, J=8Hz), 6.61(1H, t, J=8Hz), 7.03(1H, t, J=8Hz), 7.05(1H, d, J=8Hz), 7.21(2H, d, J=8Hz), 7.28(2H, d, J=8Hz).

Next, oxalic acid (18 mg) was added to the above free compound followed by recrystallization from a solvent mixture of acetone with water to give the oxalate of the title compound.
m.p. (oxalate): 199°C.

FAB-Mass: 414(MH+).

Example 39: Synthesis of 1-[1-(4-propionylaminomethylphenethyl)piperidin-4-yl]-3-methylindoline



1-[1-(4-Aminomethylphenethyl)piperidin-4-yl]-3-methylindoline (0.1 g) and propionyl chloride (0.028 ml) were treated as in Example 36 to give the title compound (0.122 g) as a pale yellow oil (yield: quantitative).

Next, oxalic acid (13 mg) was added thereto followed by recrystallization from ethyl acetate to give the oxalate (0.064 g) of the title compound as colorless crystals.

m.p. (oxalate): 96 - 105°C

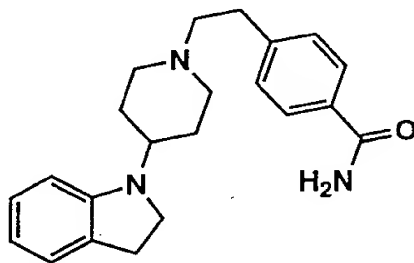
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.02(3H, t, J=8.4Hz), 1.86(2H, m), 2.10(2H, m), 2.13(2H, q, J=8.4Hz), 2.81(2H, m), 2.88(2H, t, J=8.4Hz), 2.91(2H, m), 3.07(2H, m), 3.10(2H, t, J=8.4Hz), 3.49(2H, br-d), 3.64(1H, m), 4.22(2H, s), 6.52(2H, m), 7.01(2H, m), 7.20(4H, m).

FAB-Mass: 392(MH⁺).

Example 40: Synthesis of 1-[1-(4-carbamoylphenethyl)piperidin-4-yl]indoline



4-Carbamoylphenethyl bromide (0.135 g) was treated as in Example 2 to give the title compound (0.097 g) as pale yellow crystals (yield: 56.6%).

Next, oxalic acid (13 mg) was added thereto to give the amorphous oxalate of the title compound.

m.p. (oxalate): 178 - 193°C.

Oxalate

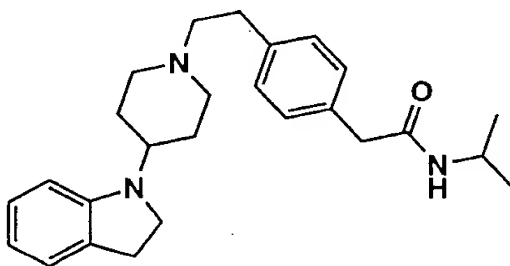
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.78(4H, m), 2.61(2H, m), 2.87(2H, t, J=8.4Hz), 2.94(4H, m), 3.31(2H, t, J=8.4Hz), 3.34(2H, m), 3.55(1H, m).

6.48(1H, d, J=7.6Hz), 6.53(1H, t, J=7.6Hz), 6.98(1H, t, J=7.6Hz), 7.01(1H, d, J=7.6Hz), 7.31(1H, m), 7.34(2H, d, J=8.4Hz), 7.82(2H, d, J=8.4Hz), 7.93(1H, m).

ESI-Mass: 350.1(MH+).

Example 41: Synthesis of 1-[1-(4-N-isopropylcarbamoylmethylphenethyl)piperidin-4-yl]indoline



N-Isopropyl-4-(2-bromoethyl)phenylacetamide (0.029 g) was treated as in Example 2 to give the title compound (0.040 g) as colorless crystals (yield: 92.1%).

Next, oxalic acid (5 mg) was added thereto to give the amorphous oxalate of the title compound.

m.p. (oxalate): 88 - 96°C.

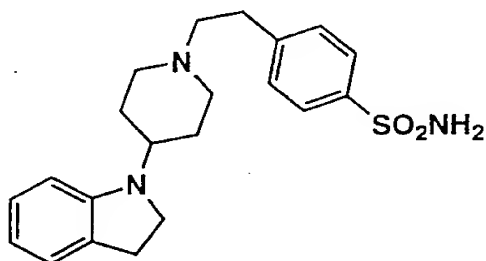
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.64(6H, d, J=6.8Hz), 1.82(4H, m), 2.82-2.92(6H, m), 3.06(2H, m), 3.31(2H, m), 3.33(2H, s), 3.46(2H, m), 3.63(1H, m), 9.79(1H, q, J=6.8Hz), 6.50(1H, d, J=8Hz), 6.54(1H, t, J=8Hz), 6.98(1H, t, J=8Hz), 7.01(1H, d, J=8Hz), 7.19(4H, s), 7.93(1H, d, J=8Hz).

ESI-Mass: 406.25(MH+).

Example 42: Synthesis of 1-[1-(4-sulfamoylphenethyl)piperidin-4-yl]indoline



1-(Piperidin-4-yl)indoline (300 mg) and 4-sulfamoylphenethyl bromide (400 mg) were treated as in Example 2 to give the title compound (60 mg) as a pale yellow powder (yield: 10%).

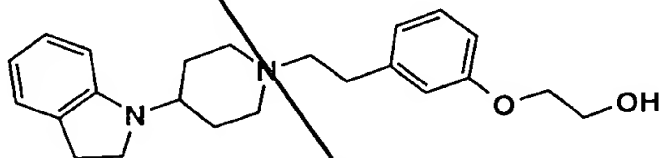
m.p.: 207 - 210°C.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.70-1.87(4H, m), 2.11-2.20(2H, m), 2.60-2.66(2H, m), 2.86-2.98(4H, m), 3.08-3.15(2H, m), 3.34-3.45(3H, m), 6.41(1H, d, J=8Hz), 6.61(1H, d, J=8Hz), 7.01-7.08(2H, m), 7.36(2H, d, J=8Hz), 7.85(2H, d, J=8Hz).

FAB-Mass: 386(MH+).

Example 43: Synthesis of 1-[3-[(2-hydroxyethoxy)phenethyl]piperidin-4-yl]indoline



7A11 3-[2-(t-Butyldimethylsilyloxy)ethoxy]phenethyl bromide (0.33 g) was treated as in Example 24 to give the title compound (0.197 g) as a yellow oil (yield: 53.8%).

Next, oxalic acid (48 mg) was added thereto to give the oxalate of the title compound.

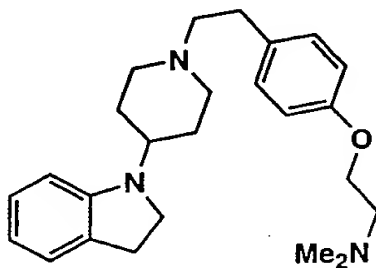
m.p. (oxalate): 118°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.86(4H, m), 2.88(2H, t, J=8.2Hz), 2.92(4H, m), 3.17(2H, m), 3.31(2H, t, J=8.2Hz), 3.53(2H, br-d), 3.67(1H, m), 3.71(2H, t, J=9.0Hz), 3.08(2H, t, J=9.0Hz), 6.52(1H, d, J=7.6Hz), 6.55(1H, t, J=7.6Hz), 6.83(2H, m), 6.87(1H, br-s), 6.99(1H, t, J=7.6Hz), 7.02(1H, d, J=7.6Hz), 7.24(1H, t, J=8.4Hz).

FAB-Mass: 367(MH+).

Example 44: Synthesis of 1-{1-[4-(2-dimethylaminoethoxy)phenethyl]piperidin-4-yl}indoline



N,N-Dimethylformamide (2.5 ml) was added to 1-[1-(4-hydroxyphenethyl)piperidin-4-yl]indoline (0.1 g), potassium carbonate (0.081 g) and 2-dimethylaminoethyl chloride

hydrochloride (0.078 g) followed by stirring at 80°C overnight (12 hr). After allowing to cool, the resultant mixture was mixed with ethyl acetate (200 ml) and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (0.052 g) as a brown oil (yield: 27.0%).

Next, hydrochloric acid was added thereto to give the hydrochloride of the title compound.

m.p. (hydrochloride): 258 - 259°C.

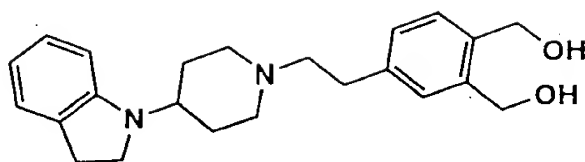
Hydrochloride

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.87(2H, m), 2.12(2H, m), 2.82(6H, m), 2.91(2H, t, J=8.4Hz), 3.06(4H, m), 3.21(2H, m), 3.34(2H, t, J=8.4Hz), 3.48(2H, m), 3.63(2H, br-d), 3.75(1H, m), 4.37(2H, t, J=4.8Hz), 6.59(1H, d, J=8.0Hz), 6.60(1H, t, J=8.0Hz), 6.98(2H, d, J=8.6Hz), 7.01(1H, t, J=8.0Hz), 7.05(1H, d, J=8.0Hz), 7.24(2H, d, J=8.6Hz).

ESI-Mass: 394.2(MH+).

Example 45: Synthesis of 1-{1-[3,4-di(hydroxymethyl)phenethyl]piperidin-4-yl}indoline



3,4-Di[(t-butyl)dimethylsilyloxymethyl]phenethyl bromide (0.421 g) was treated as in Example 24 to give the title compound (0.318 g) as a pale yellow oil (yield: 98.6%).

Next, hydrochloric acid was added thereto to give a salt followed by recrystallization from ethanol to give the hydrochloride (0.617 g) of the title compound as colorless crystals (yield: 47.1%).

m.p. (hydrochloride): 178°C.

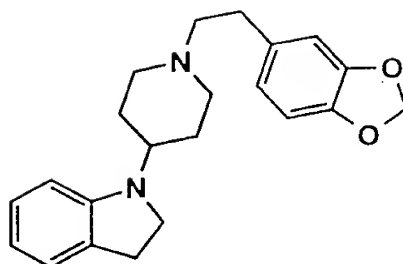
Hydrochloride

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.89(2H, m), 1.04(2H, m), 2.90(2H, t, J=8.0Hz), 3.08(4H, m), 3.25(2H, m), 3.33(2H, t, J=8.0Hz), 3.66(2H, br-d), 3.73(1H, m), 4.50(2H, s), 4.53(2H, s), 6.55(1H, d, J=7.6Hz), 6.58(1H, t, J=7.6Hz), 7.01(1H, t, J=7.6Hz), 7.04(1H, d, J=7.6Hz), 7.14(1H, dd, J=1.6, 8.0Hz), 7.32(1H, d, J=1.6Hz), 7.34(1H, d, J=8.0Hz).

FAB-Mass: 367(MH+).

Example 46: Synthesis of 1-[1-[3,4-(methylenedioxy)phenethyl]piperidin-4-yl]indoline



3,4-(Methylenedioxy)phenylacetic acid (0.198 g) was treated as in Example 11 to give the title compound (0.304 g) as a colorless oil (yield: 89.8%).

Next, hydrochloric acid was added thereto to give a salt followed by recrystallization from ethanol to give the hydrochloride of the title compound as colorless crystals.

m.p. (hydrochloride): 236°C.

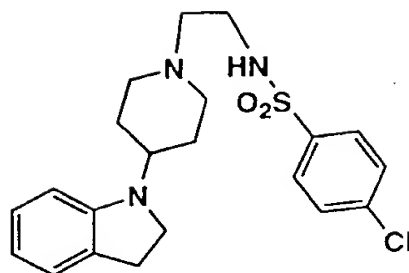
Hydrochloride

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.88(2H, br-d), 2.12(2H, m), 2.93(2H, t, J=8.0Hz), 3.03(4H, m), 3.20(2H, m), 3.37(2H, t, J=8.0Hz), 3.61(2H, br-d), 3.78(1H, m), 5.99(2H, s), 6.74(1H, d, J=8.0Hz), 6.88(2H, m), 7.06(2H, m).

FAB-Mass: 361(MH+).

Example 47: Synthesis of 1-[1-[2-(4-chlorophenylsulfonylamino)ethyl]piperidin-4-yl]indoline



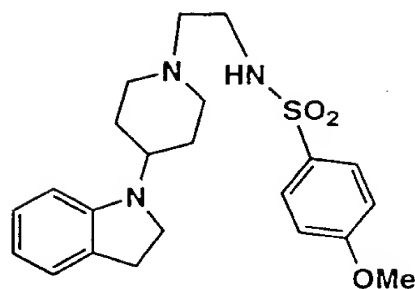
1-[1-(2-Aminoethyl)piperidin-4-yl]indoline (113 mg) was dissolved in chloroform (3 ml). Under ice cooling, 4-chlorobenzenesulfonyl chloride (97 mg) was added thereto and the resultant mixture was stirred for 6 hr. After adding water, the reaction solution was extracted with chloroform. The organic layer was washed with brine and dried over magnesium sulfate. After evaporating the solvent, the resulting residue (205 mg) was purified by NH-silica gel column chromatography (methanol/methylene chloride system) to give the title compound (134 mg) as an oil.

$^1\text{H-NMR}$ (400 MHz, CDCl_3):

$\delta(\text{ppm})$ 1.54-1.66(2H, m), 1.71-1.78(2H, m), 1.99-2.07(2H, m), 2.42(2H, t, $J=5.8\text{Hz}$), 2.70-2.76(2H, m), 2.94-3.02(4H, m), 3.28-3.40(3H, m), 5.30(1H, br-s), 6.36(1H, d, $J=8.0\text{Hz}$), 6.59-6.63(1H, m), 7.00-7.08(2H, m), 7.47-7.52(2H, m), 7.80-7.84(2H, m).

FAB-Mass: 420(MH $^+$).

Example 48: Synthesis of 1-[1-[2-(4-methoxyphenylsulfonylamino)ethyl]piperidin-4-yl]indoline



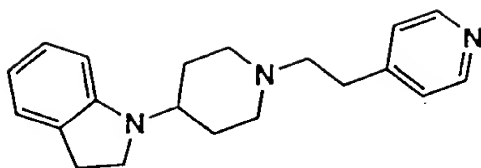
1-[1-(2-Aminoethyl)piperidin-4-yl]indoline (113 mg) was dissolved in chloroform (3 ml). Under ice cooling, 4-methoxybenzenesulfonyl chloride (95 mg) was added thereto and the resultant mixture was stirred at room temperature overnight. After adding water, the reaction solution was extracted with chloroform. The organic layer was washed with brine and dried over magnesium sulfate. After evaporating the solvent, the resulting residue (80 mg) was purified by NH-silica gel column chromatography (methanol/methylene chloride system) to give the title compound (45 mg) as an oil.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.54-1.76(4H, m), 1.96-2.04(2H, m), 2.40(2H, t, J=5.8Hz), 2.67-2.74(2H, m), 2.93-3.00(4H, m), 3.27-3.36(1H, m), 3.37(2H, t, J=8.4Hz), 3.86(3H, s), 5.19(1H, br-s), 6.36(1H, d, J=8.0Hz), 6.58-6.62(1H, m), 6.95-7.08(4H, m), 7.78-7.83(2H, m).

FAB-Mass: 416(MH⁺).

Example 49: Synthesis of 1-[1-[2-(4-pyridyl)ethyl]piperidin-4-yl]indoline



1-(4-Piperidyl)indoline (0.1 g) was dissolved in ethanol (5 ml). After adding 4-vinylpyridine (0.16 ml), the resultant mixture was heated under reflux in a nitrogen atmosphere for 12 hr. Then the reaction solution was concentrated under reduced pressure and purified by silica gel column chromatography (toluene/acetone system) to give the title compound (0.064 g) as a colorless oil (yield: 42.5%).

Free

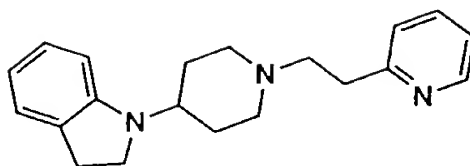
$^1\text{H-NMR}$ (400 MHz, CDCl_3):

δ (ppm) 1.74-1.85(4H, m), 2.15(2H, dt, $J=2.8, 12.0\text{Hz}$), 2.64(2H, m), 2.82(2H, m), 2.95(2H, t, $J=8.4\text{Hz}$), 3.10(2H, br-d), 3.39(2H, t, $J=8.4\text{Hz}$), 3.40(1H, m), 6.41(1H, d, $J=8.0\text{Hz}$), 6.61(1H, t, $J=8.0\text{Hz}$), 7.04(1H, t, $J=8.0\text{Hz}$), 7.05(1H, d, $J=8.0\text{Hz}$), 7.14(2H, dd, $J=2.0, 4.8\text{Hz}$), 8.50(2H, dd, $J=2.0, 4.8\text{Hz}$).

Next, hydrochloric acid was added to the above product to give the hydrochloride of the title compound as a hygroscopic pale yellow amorphous solid.

FAB-Mass: 308(MH+).

Example 50: Synthesis of 1-{1-[2-(2-pyridyl)ethyl]piperidin-4-yl}indoline



2-Vinylpyridine (0.16 ml) was treated as in Example 49 to give the title compound (0.041 g) as a colorless oil (yield: 27.2%).

Next, hydrochloric acid was added thereto to give a salt followed by recrystallization from ethanol-isopropyl ether mixtures to give the hydrochloride (0.036 g) of the title compound.

m.p. (hydrochloride): 258 - 260°C.

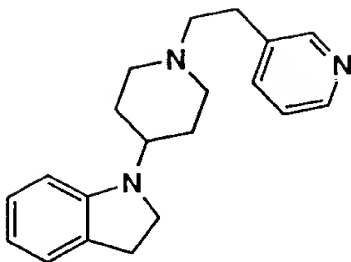
Hydrochloride

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.89(2H, br-d), 2.16(2H, m), 2.93(2H, t, J=8.0Hz), 3.20(2H, m), 3.38(2H, t, J=8.0Hz), 3.61(6H, m), 3.83(1H, br-t), 6.66(2H, m), 7.05(1H, t, J=8Hz), 7.08(1H, d, J=8Hz), 7.89(1H, m), 8.00(1H, d, J=7.6Hz), 8.47(1H, m), 8.82(1H, d, J=5.2Hz).

FAB-Mass: 308(MH+).

Example 51: Synthesis of 1-{1-[2-(3-pyridyl)ethyl]piperidin-4-yl}indoline



3-(2-Bromoethyl)pyridine (0.481 g) was treated as in Example 2 to give the title compound (0.601 g) as a pale yellow oil (yield: 75.5%).

Next, oxalic acid was added thereto to give a salt followed by recrystallization from ethanol to give the oxalate of the title compound.

m.p. (oxalate): 174°C.

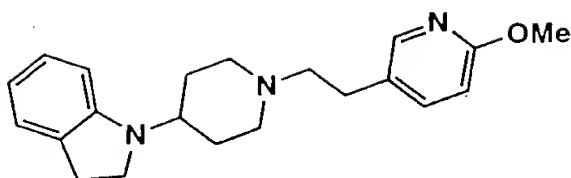
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.92(4H, m), 2.87(2H, t, J=8.4Hz), 3.04(4H, m), 3.10(2H, m), 3.31(2H, t, J=8.4Hz), 3.61(2H, br-d), 3.72(1H, m), 6.53(1H, d, J=7.6Hz), 6.56(1H, t, J=7.6Hz), 7.00(1H, t, J=7.6Hz), 7.03(1H, d, J=7.6Hz), 7.39(1H, dd, J=4.8, 7.6Hz), 7.74(1H, ddd, J=1.6, 1.6, 7.6Hz), 8.48(1H, dd, J=1.6, 4.8Hz), 8.53(1H, J=1.6Hz).

ESI-Mass: 308(MH⁺).

Example 52: Synthesis of 1-{1-[2-(2-methoxy-5-pyridyl)ethyl]piperidin-4-yl}indoline



1-Bromo-2-(2-methoxypyridin-5-yl)ethane (1.221 g) was treated as in Example 2 to give the title compound (1.394 g) as a pale yellow oil (yield: 82.6%).

Next, oxalic acid (0.372 g) was added thereto to give a salt followed by recrystallization from ethanol to give the oxalate of the title compound.

m.p. (oxalate): 173°C.

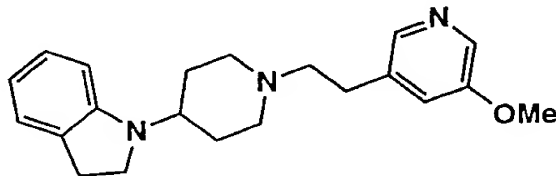
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.83-1.95(4H, br-d), 2.88(2H, t, J=8.4Hz), 2.94 (4H, m), 3.15(2H, m), 3.31(2H, t, J=8.4Hz), 3.53(2H, br-d), 3.68(1H, m), 3.83(3H, s), 6.52(1H, d, J=8.0Hz), 6.55(1H, t, J=8.0Hz), 6.81(1H, d, J=8.4Hz), 6.99(1H, t, J=8.0Hz), 7.02(1H, d, J=8.0Hz), 7.64(1H, dd, J=2.4, 8.4Hz), 8.08(1H, d, J=2.4Hz).

FAB-Mass; 338(MH⁺).

Example 53: Synthesis of 1-{1-[2-(3-methoxypyridin-5-yl)]-ethyl}piperidin-4-yl}indoline



5-(2-Bromoethyl)-3-methoxypyridine (0.181 g) was treated

as in Example 2 to give the title compound (1.104 g) as a yellow oil (yield: 37.1%).

Next, oxalic acid (28 mg) was added thereto to give a salt followed by recrystallization from ethanol to give the oxalate (0.077 g) of the title compound.

m.p. (oxalate): 220°C.

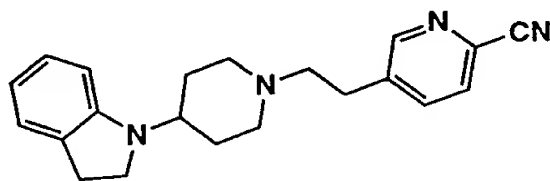
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.89(4H, m), 2.88(2H, t, J=8.4Hz), 3.99(2H, m), 3.22(2H, m), 3.31(2H, t, J=8.4Hz), 3.54(2H, br-d), 3.68(1H, m), 3.83(3H, s), 6.52(1H, d, J=7.6Hz), 6.55(1H, t, J=7.6Hz), 6.99(1H, t, J=7.6Hz), 7.02(1H, d, J=7.6Hz), 7.35(1H, t, J=2.0Hz), 8.11(1H, t, J=2.0Hz), 8.19(1H, t, J=2.0Hz).

FAB-Mass: 338(MH+).

Example 54: Synthesis of 1-{1-[2-(2-cyanopyridin-5-yl)ethyl]piperidin-4-yl}indoline



1-Bromo-2-(2-cyanopyridin-5-yl)ethane (0.406 g) was treated as in Example 2 to give the title compound (0.068 g) as a pale yellow oil (yield: 9.7%).

Next, oxalic acid (18 mg) was added thereto to give a salt

followed by recrystallization from ethanol to give the oxalate of the title compound.

m.p. (oxalate): 136°C.

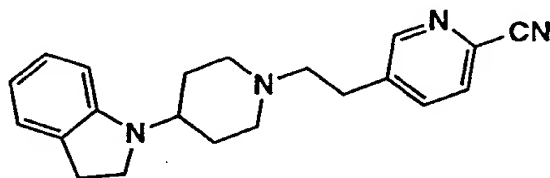
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.82(4H, m), 2.81(2H, m), 2.87(2H, t, J=8.2Hz), 3.07(2H, m), 3.14(2H, m), 3.31(2H, t, J=8.2Hz), 3.44(2H, br-d), 3.63(1H, m), 6.51(1H, d, J=7.6Hz), 6.54(1H, t, J=7.6Hz), 6.99(1H, t, J=7.6Hz), 7.01(1H, d, J=7.6Hz), 8.01(2H, m), 8.71(1H, d, J=1.6Hz).

FAB-Mass: 333(MH+).

Example 55: Synthesis of 1-{1-[2-(2-hydroxymethylpyridin5-yl)ethyl]piperidin-4-yl}indoline



1-{1-[2-(2-Cyanopyridin-5-yl)ethyl]piperidin-4-yl}indoline (0.103 g) was dissolved in toluene (1.5 ml). In a nitrogen atmosphere at -78°C, a 1.5 M solution (0.44 ml) of diisobutylaluminum hydride in toluene was added thereto and the resultant mixture was stirred under the same conditions for 1 hr. Then the reaction solution was poured into a 5% aqueous solution of sulfuric acid and basified with an aqueous solution of sodium hydroxide. Next, diethyl ether was added and the

layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound (0.066 g) as a yellow oil (yield: 64.5%).

Free

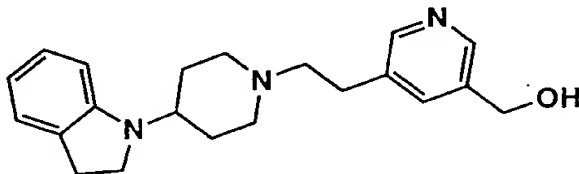
¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.79(4H, m), 2.13(2H, dt, J=2.8, 8.0Hz), 2.60(2H, m), 2.80(2H, m), 2.97(2H, d, J=8.4Hz), 3.10(2H, br-d), 3.39(2H, t, J=8.4Hz), 3.40(1H, m), 3.95(2H, s), 6.41(1H, d, J=7.6Hz), 6.60(1H, t, J=7.6Hz), 7.04(1H, t, J=7.6Hz), 7.05(1H, d, J=7.6Hz), 7.21(1H, d, J=8.0Hz), 7.50(1H, dd, J=2.0, 8.0Hz), 8.42(1H, d, J=2.0Hz).

ESI-Mass: 338.3(MH⁺).

Next, oxalic acid (18 mg) was added to the above product to give the oxalate of the title compound as a hygroscopic amorphous solid.

Example 56: Synthesis of 1-{1-[2-(3-hydroxymethylpyridin-5-yl)ethyl]piperidin-4-yl}indoline



5-(2-Bromoethyl)-3-(t-butyl)dimethylsilyloxymethylpyridine (0.248g) was treated as in Example 24 to give the title compound (0.150 g) as a pale yellow oil (yield: 61.4%).

Next, oxalic acid (40 mg) was added thereto to give a salt followed by recrystallization from ethanol to give the oxalate (0.143 g) of the title compound.

m.p. (oxalate): 177°C.

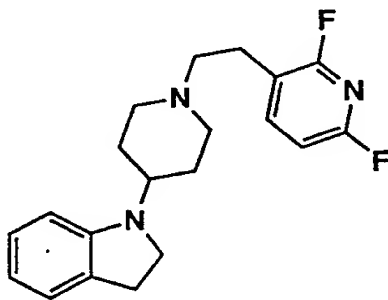
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.89(4H, m), 2.88(2H, t, J=8.4Hz), 3.01(2H, m), 3.22(2H, m), 3.32(2H, t, J=8.4Hz), 3.57(2H, br-d), 3.69(1H, m), 4.53(2H, s), 6.53(1H, d, J=7.6Hz), 6.56(1H, t, J=7.6Hz), 6.99(1H, t, J=7.6Hz), 7.02(1H, d, J=7.6Hz), 7.66(1H, s), 8.39(1H, d, J=1.8Hz), 8.41(1H, d, J=1.8Hz).

FAB-Mass: 338(MH⁺).

Example 57: Synthesis of 1-[1-(2,6-difluoro-3-pyridylethyl)piperidin-4-yl]indoline



1-(Piperidin-4-yl)indoline (300 mg) and 2,6-difluoro-3-bromoethylpyridine (330 mg) were treated as in Example 2 to give the hydrochloride (270 mg) of the title compound as a white powder (yield: 47%).

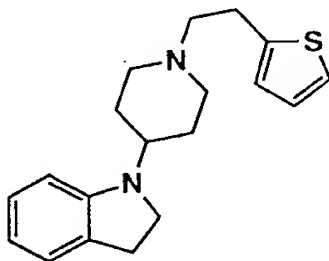
m.p. (hydrochloride): 202 - 204°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.82-1.91(2H, m), 2.00-2.13(2H, m), 2.88(2H, t, J=8Hz), 3.03-3.16(4H, m), 3.24-3.34(4H, m), 3.58-3.66(2H, m), 3.68-3.78(1H, m), 6.54-6.61(2H, m), 6.96-7.05(2H, m), 7.17-7.22(1H, m), 8.10-8.18(1H, m).

FAB-Mass: 344(MH⁺).

Example 58: Synthesis of 1-{1-[2-(2-thienyl)ethyl]piperidin-4-yl}indoline



1-(4-Piperidyl)indoline (0.1 g) was treated as in Example 2 to give the title compound (0.057 g) as colorless crystals (yield: 37.2%).

Next, hydrochloric acid was added thereto to give a salt followed by recrystallization from ethanol-isopropyl ether mixtures to give the hydrochloride of the title compound as colorless crystals.

m.p. (hydrochloride): 243°C.

Hydrochloride

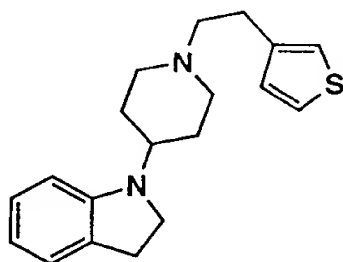
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.88(2H, br-d), 2.15(2H, m), 2.93(2H, t, J=8.4Hz), 3.09(2H, m), 3.34(6H, m), 3.64(2H, br-d), 3.78(1H, tt, J=3.6,

12Hz), 6.66(2H, m), 7.00(2H, m), 7.06(2H, m), 7.42(1H, dd, J=1.2, 4.8Hz).

FAB-Mass: 313(MH+).

Example 59: Synthesis of 1-{1-[2-(3-thienyl)ethyl]piperidin-4-yl}indoline



3-(2-Bromoethyl)thiophene (0.19 g) was treated as in Example 2 to give the title compound (0.105 g) as a colorless oil (yield: 68.6%).

Next, hydrochloric acid was added thereto to give a salt followed by recrystallization from ethanol-isopropyl ether mixtures to give the hydrochloride of the title compound as colorless crystals.

m.p. (hydrochloride): 248°C.

Hydrochloride

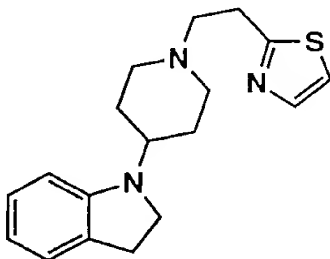
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.88(2H, br-d), 2.04(2H, m), 2.90(2H, t, J=8.4Hz), 3.08(4H, m), 3.30(2H, m), 3.32(2H, t, J=8.4Hz), 3.63(2H, br-d), 3.74(1H, m), 6.56(1H, d, J=7.6Hz), 6.58(1H, t, J=7.6Hz), 7.00(1H, t, J=7.6Hz), 7.04(1H, d, J=7.6Hz), 7.08(1H, dd, J=1.2,

4.8Hz), 7.34(1H, m), 7.55(1H, dd, J=2.8, 4.8Hz).

FAB-Mass: 313(MH+).

Example 60: Synthesis of 1-[1-(2-thiazolylethyl)piperidin-4-yl]indoline



2-(2-Bromoethyl)thiazole (0.46 g) was treated as in Example 2 to give the title compound (0.102 g) as colorless crystals (yield: 14.4%).

Next, oxalic acid (15 mg) was added thereto to give a salt followed by recrystallization from ethanol-acetone mixtures to give the oxalate of the title compound as colorless crystals. m.p. (oxalate): 149°C.

Oxalate

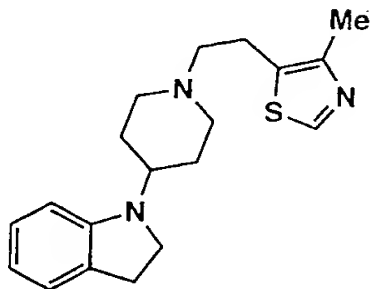
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.85(2H, m), 2.86(2H, m), 2.87(2H, t, J=8.4Hz), 3.30(2H, m), 3.31(2H, t, J=8.4Hz), 3.40(4H, m), 3.47(2H, br-d), 3.63(1H, m), 6.50(1H, d, J=7.6Hz), 6.55(1H, t, J=7.6Hz), 6.99(1H, t, J=7.6Hz), 7.02(1H, d, J=7.6Hz), 7.65(1H, d, J=3.6Hz), 7.75(1H, d, J=3.6Hz).

FAB-Mass: 314(MH+).

Example 61: Synthesis of 1-[1-(4-methyl-5-

thiazolethyl)piperidin-4-yl}indoline



1-(Piperidin-4-yl)indoline (300 mg) and 4-methyl-5-thiazolethyl bromide (310 mg) obtained in the same manner as the one of Production Example 1 were treated as in Example 2 to give the hydrochloride (140 mg) of the title compound as a gray powder (yield: 26%).

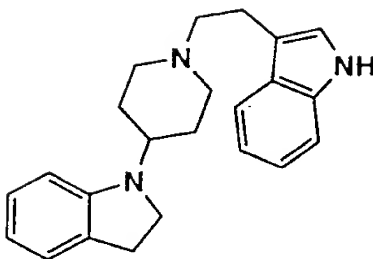
m.p. (hydrochloride): 222 - 225°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.82-1.89(2H, m), 1.95-2.10(2H, m), 2.37(3H, s), 2.87(2H, t, J=8Hz), 3.01-3.12(2H, m), 3.15-3.33(6H, m), 3.60-3.76(3H, m), 6.51-6.60(2H, m), 6.95-7.03(2H, m), 8.93(1H, s).

FAB-Mass: 328(MH+).

Example 62: Synthesis of 1-{1-[(indol-3-yl)ethyl]-piperidin-4-yl}indoline



1-(Piperidin-4-yl)indoline (300 mg) and 3-(2-bromoethyl)indole (340 mg) obtained in the same manner as the one of Production Example 1 were treated as in Example 2 to give the hydrochloride (410 mg) of the title compound as a brown powder (yield: 72%).

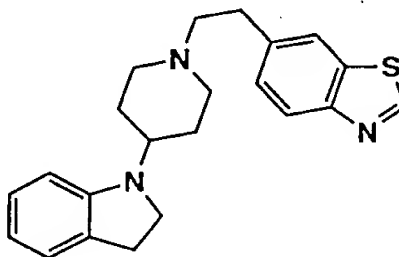
m.p. (hydrochloride): 240°C (decomp.).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.82-1.91(2H, m), 1.93-2.08(2H, m), 2.89(2H, t, J=8Hz), 3.07-3.20(4H, m), 3.27-3.36(4H, m), 3.65-3.76(3H, m), 6.51-6.58(2H, m), 6.96-7.04(3H, m), 7.06-7.11(1H, m), 7.24(1H, s), 7.35(1H, d, J=8Hz), 7.61(1H, d, J=8Hz).

FAB-Mass: 346(MH+).

Example 63: Synthesis of 1-{1-[2-(6-benzothiazolyl)]-ethyl}piperidin-4-yl}indoline



6-(2-Bromoethyl)benzothiazole (0.073 g) was treated as in Example 2 to give the title compound (0.084 g) as a pale yellow oil (yield: 70.0%).

Next, oxalic acid (21 mg) was added thereto to give a salt followed by recrystallization from ethanol to give the oxalate of the title compound.

m.p. (oxalate): 197°C.

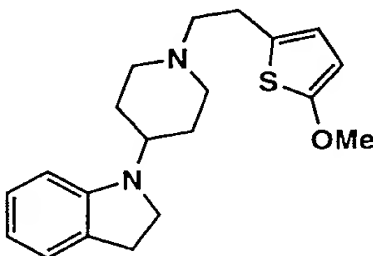
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.87(4H, m), 2.88(2H, t, J=8.4Hz), 2.95(2H, m), 3.13(2H, m), 3.25(2H, m), 3.32(2H, t, J=8.4Hz), 3.56(2H, m), 3.68(1H, m), 6.52(1H, d, J=8.0Hz), 6.55(1H, t, J=8.0Hz), 6.99(1H, t, J=8.0Hz), 7.02(1H, d, J=8.0Hz), 7.48(1H, dd, J=1.6, 8.4Hz), 8.06(1H, d, J=8.4Hz), 8.09(1H, d, J=1.6Hz), 9.37(1H, s).

FAB-Mass: 364(MH+).

Example 64: Synthesis of 1-[1-(5-methoxy-2-thienyl)ethylpiperidin-4-yl]indoline



1-(Piperidin-4-yl)indoline (300 mg) and (5-methoxy-2-thienyl)ethyl bromide (400 mg) were treated as in Example 2 to

give the hydrochloride (260 mg) of the title compound as a white powder (yield: 46%).

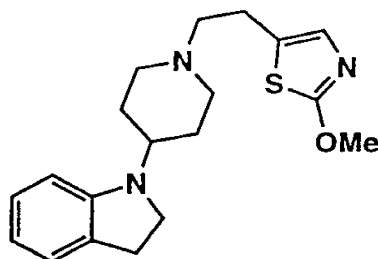
m.p. (hydrochloride): 204°C (decomp.).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.80-1.89(2H, m), 2.00-2.11(2H, m), 2.90(2H, t, J=8Hz), 3.00-3.28(6H, m), 3.32(2H, t, J=8Hz), 3.55-3.62(2H, m), 3.67-3.78(1H, m), 3.80(3H, s), 6.13(1H, d, J=4Hz), 6.56-6.60(3H, m), 6.97-7.04(2H, m), 10.79(1H, br-s).

FAB-Mass: 343(MH+).

Example 65: Synthesis of 1-[1-(2-methoxy-5-thiazolyl)ethyl]piperidin-4-ylindoline



1-(Piperidin-4-yl)indoline (300 mg) and (2-methoxy-5-thiazolyl)ethyl bromide (380 mg) were treated as in Example 2 to give the hydrochloride (340 mg) of the title compound as a white powder (yield: 60%).

m.p. (hydrochloride): 207°C (decomp.).

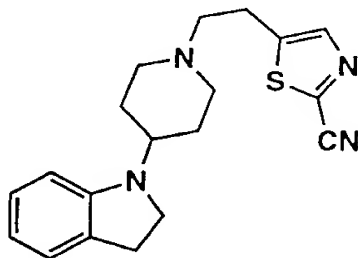
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.80-1.86(2H, m), 1.92-2.03(2H, m), 2.89(2H, t, J=8Hz), 3.00-3.12(2H, m), 3.15-3.32(6H, m), 3.67-3.75(3H, m), 3.95(3H, s), 6.50-6.59(2H, m), 6.94-7.07(3H, m), 10.36(1H,

br-s).

FAB-Mass: 344(MH+).

Example 66: Synthesis of 1-[1-(2-cyano-5-thiazolyl)ethylpiperidin-4-yl]indoline



1-(Piperidin-4-yl)indoline (190 mg) and (2-cyano-5-thiazolyl)ethyl bromide (200 mg) were treated as in Example 2 to give the hydrochloride (21 mg) of the title compound as a gray powder (yield: 6.1%).

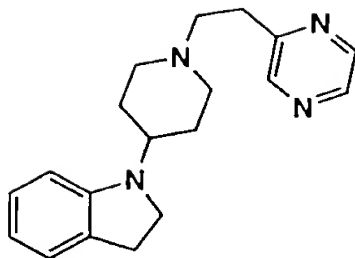
m.p. (hydrochloride): 209 - 211°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.81-2.00(4H, m), 2.89(2H, t, J=8Hz), 3.01-3.15(2H, m), 3.30(2H, t, J=8Hz), 3.36-3.78(7H, m), 6.49-6.55(2H, m), 6.92-7.03(2H, m), 8.02(1H, s).

FAB-Mass: 339(MH+).

Example 67: Synthesis of 1-(1-pyrazinylethylpiperidin-4-yl)indoline



A solution of 1-(piperidin-4-yl)indoline (500 mg) and vinylpyrazine (260 mg) in o-dichlorobenzene (5 ml) was heated at 180°C for 3 hr. Next, the reaction solution was purified by silica gel column chromatography (methylene chloride/ethanol system) and treated in a conventional manner so as to give the oxalate (90 mg) of the title compound as a white powder (yield: 9.0%).

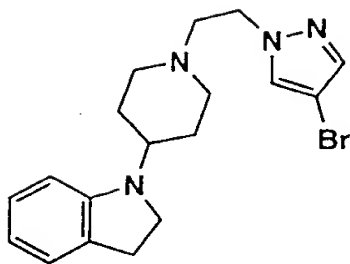
m.p. (oxalate): 168 - 170°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.75-1.83(4H, m), 2.80-2.91(4H, m), 3.11-3.20(2H, m), 3.21-3.33(4H, m), 3.41-3.52(2H, m), 3.55-3.69(1H, m), 6.48(1H, d, J=8Hz), 6.53(1H, t, J=8Hz), 6.95-7.00(2H, m), 8.53(1H, s), 8.57-8.59(1H, m), 8.63(1H, s).

FAB-Mass: 309(MH+).

Example 68: Synthesis of 1-{1-[2-(4-bromopyrazol-1-yl)ethyl]piperidin-4-yl}indoline



1-(4-Piperidyl)indoline (162 mg) and 1-(2-bromoethyl)-4-bromopyrazole (200 mg) were treated as in Example 2 to give the hydrochloride (372 mg) of the title compound as beige crystals (yield: 67%).

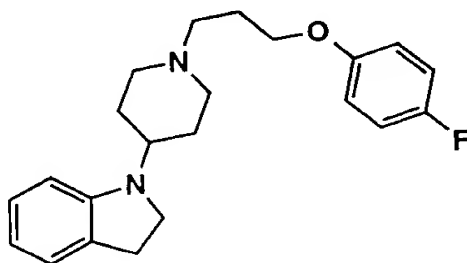
m.p. (hydrochloride): 210 - 212°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.83(2H, d, J=11.6Hz), 2.00-2.12(2H, m), 2.88(2H, t, J=8.4Hz), 3.07(2H, q, J=11.2Hz), 3.31(2H, t, J=8.4Hz), 3.46-3.54(4H, m), 3.66-3.76(1H, m), 4.63(2H, t, J=6.8Hz), 6.56-6.64(2H, m), 6.97-7.06(2H, m), 7.64(1H, s), 8.11(1H, s), 11.10(1H, br-s).

ESI-Mass: 351(MH⁺).

Example 69: Synthesis of 1-{1-[3-(4-fluorophenoxy)propyl]piperidin-4-yl}indoline



1-(Piperidin-4-yl)indoline (300 mg) and 1-bromo-3-(4-fluorophenoxy)propane (420 mg) were treated as in Example 2 to give the hydrochloride (330 mg) of the title compound as white needles (yield: 56%).

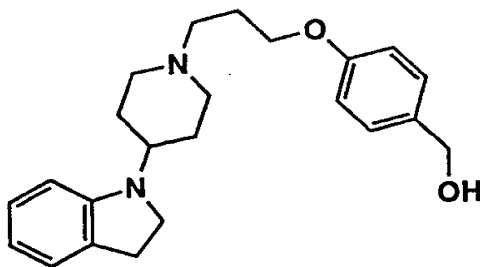
m.p. (hydrochloride): 207 - 210°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.80-1.87(2H, m), 1.91-2.20(4H, m), 2.88(2H, t, J=8Hz), 3.00-3.11(2H, m), 3.13-3.21(2H, m), 3.30(2H, t, J=8Hz), 3.52-3.61(2H, m), 3.66-3.77(1H, m), 4.04(2H, t, J=6Hz), 6.49-6.70(2H, m), 6.92-7.03(4H, m), 7.08-7.15(2H, m).

FAB-Mass: 355(MH⁺).

Example 70: Synthesis of 1-{1-[3-(4-hydroxymethylphenoxy)propyl]piperidin-4-yl}indoline



1-(4-Piperidyl)indoline (263 mg) and 4-(3-bromopropoxy)benzyl alcohol (389 mg) were treated as in Example 2 to give the title compound (422 mg) as a pale orange amorphous solid (yield: 92%).

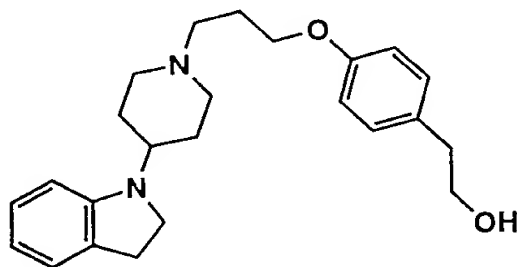
¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 2.20-2.35(4H, m), 2.47-2.73(4H, m), 2.55(2H, t,

J=7.4Hz), 2.94(2H, t, J=8.4Hz), 3.07(2H, d, J=11.2Hz), 3.35-3.43(1H, m), 3.38(2H, t, J=8.4Hz), 4.02(2H, t, J=6.4Hz), 4.62(2H, s), 6.41(1H, d, J=8Hz), 6.60(1H, dt, J=7.4Hz, 0.8Hz), 6.89(2H, d, J=8.8Hz), 7.04(1H, ddd, J=8Hz, 7.4Hz, 0.8Hz), 7.05(1H, d, J=7.4Hz), 7.29(2H, d, J=8.8Hz).

ESI-Mass: 367(MH+).

Example 71: Synthesis of 1-{1-[3-(4-hydroxyethylphenoxy)propyl]piperidin-4-yl}indoline



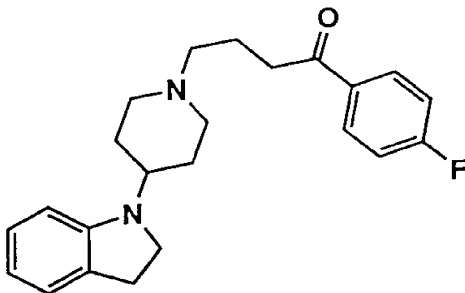
1-(4-Piperidyl)indoline (303 mg) and 4-(3-bromopropoxy)phenethyl alcohol (389 mg) were treated as in Example 2 to give the hydrochloride (500 mg) of the title compound as a beige amorphous solid (yield: 80%).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.84(2H, d, J=13.2Hz), 2.40-2.22(4H, m), 2.63(2H, t, J=7.2Hz), 2.90(2H, t, J=8.4Hz), 3.05(2H, q, J=10.4Hz), 3.12-3.19(2H, m), 3.33(2H, t, J=8.4Hz), 3.52(2H, t, J=7.2Hz), 3.52-3.60(2H, m), 3.70-3.80(1H, m), 4.01(2H, t, J=6Hz), 6.58-6.68(2H, br-t), 6.83(2H, d, J=8.8Hz), 7.01(1H, d, J=8Hz), 7.05(1H, d, J=8Hz), 7.11(2H, d, J=8.8Hz), 10.80(1H, br-s).

ESI-Mass: 381(MH+).

Example 72: Synthesis of 1-{1-[4-(4-fluorophenyl)-4-oxobutyl]piperidin-4-yl}indoline



1-(Piperidin-4-yl)indoline (1.0 g) and 4-chloro-1-(4-fluorophenyl)-1-butanone (1.1 g) were treated as in Example 2 to give the title compound (0.5 g) (yield: 27%).

A portion of this product was then treated in a conventional manner so as to give the hydrochloride of the title compound as a white powder.

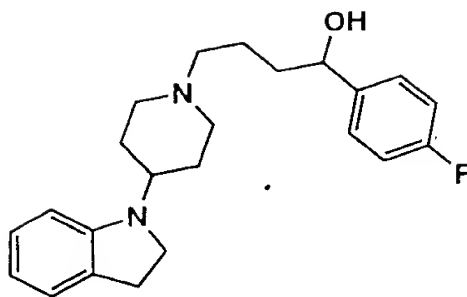
m.p. (hydrochloride): 213°C (decomp.).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.80-1.88(2H, m), 1.94-2.10(4H, m), 2.88(2H, t, J=8Hz), 3.00-3.10(4H, m), 3.19(2H, t, J=8Hz), 3.30(2H, t, J=8Hz), 3.50-3.60(2H, m), 3.67-3.78(1H, m), 6.52-6.58(2H, m), 6.96-7.03(2H, m), 7.34-7.39(2H, m), 8.03-8.07(2H, m).

FAB-Mass: 367(MH+).

Example 73: Synthesis of 1-{1-[4-(4-fluorophenyl)-4-hydroxybutyl]piperidin-4-yl}indoline



Sodium borohydride (38 mg) was added to a solution of 1-{1-[4-(4-fluorophenyl)-4-oxobutyl]piperidin-4-yl}indoline (320 mg) in ethanol (20 ml) and the resultant mixture was stirred for 5 hr. After concentrating under reduced pressure, water and ethyl acetate were added thereto and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Then the residue was purified by silica gel column chromatography (hexane/ethyl acetate system) and treated in a conventional manner so as to give the hydrochloride (250 mg) of the title compound as a gray powder (yield: 71%).

m.p. (hydrochloride): 174 - 175°C.

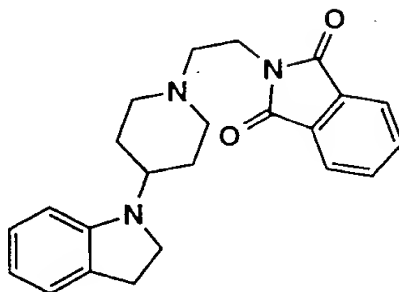
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.55-2.00(6H, m), 2.87(2H, t, J=8Hz), 2.95-3.05(4H, m), 3.28(2H, t, J=8Hz), 3.46-3.54(2H, m), 3.62-3.71(1H, m), 4.57(1H, t, J=6Hz), 6.49-6.56(2H, m), 6.95-7.02(2H, m), 7.11-7.16(2H, m), 7.34-7.38(2H, m), 9.71(1H, br-s).

FAB-Mass: 369(MH⁺).

Example 74: Synthesis of 1-[1-(phthalimido-1-

yl)ethylpiperidin-4-yl)indoline

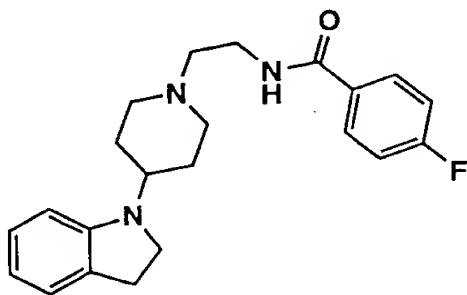


1-(Piperidin-4-yl)indoline (500 mg) and N-(2-bromoethyl)phthalimide (750 mg) were treated as in Example 2 to give the title compound (520 mg) as a colorless oil (yield: 55%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.59-1.81(4H, m), 2.09-2.20(2H, m), 2.68(2H, t, J=7Hz), 2.90(2H, t, J=8Hz), 3.08-3.15(2H, m), 3.30-3.41(1H, m), 3.32(2H, t, J=8Hz), 3.83(2H, t, J=7Hz), 6.38(1H, d, J=8Hz), 6.59(1H, t, J=8Hz), 7.00-7.08(2H, m), 7.68-7.73(2H, m), 7.80-7.87(2H, m).

Example 75: Synthesis of 1-[1-(4-fluorobenzamido)ethylpiperidin-4-yl)indoline



A solution of 1-[1-(phthalimido-1-yl)ethylpiperidin-

4-yl]indoline (520 mg) and hydrazine (100 mg) in ethanol (20 ml) was heated under reflux for 5 hr. After cooling to room temperature, the resulting crystalline precipitates were filtered off and the filtrate was concentrated. The resulting residue was mixed with methylene chloride (30 ml), a 2 N aqueous solution (5 ml) of sodium hydroxide and 4-fluorobenzoyl chloride (250 mg) followed by vigorously stirring the resultant mixture at room temperature. After 1 hr, the reaction solution was diluted with methylene chloride and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and purified by silica gel column chromatography (methylene chloride/ethanol system) followed by conversion into a hydrochloride. Thus the hydrochloride (160 mg) of the title compound was obtained as a white powder (yield: 28%).

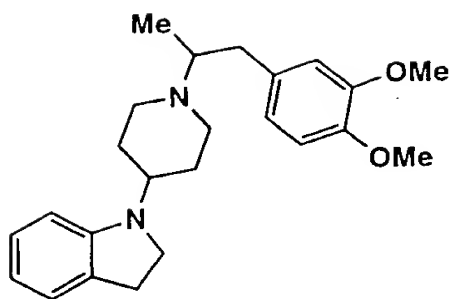
m.p. (hydrochloride): 221°C (decomp.).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.81-2.02(4H, m), 2.88(2H, t, J=8Hz), 3.02-3.15(2H, m), 3.20-3.31(4H, m), 3.60-3.75(5H, m), 6.49-6.56(2H, m), 6.95-7.02(2H, m), 7.29-7.34(2H, m), 7.94-7.99(2H, m), 8.86(1H, t, J=6Hz).

FAB-Mass: 368(MH+).

Example 76: Synthesis of 1-{1-[1-(3,4-dimethoxyphenyl)propan-2-yl]piperidin-4-yl}indoline



A mixture of 1-(piperidin-4-yl)indoline (300 mg), 3,4-dimethoxyphenylacetone (870 mg), sodium cyanoborohydride (280 mg) and molecular sieve (1.0 g) in methanol (20 ml) was stirred at room temperature for 3 days. Then the reaction solution was filtered and concentrated under reduced pressure, water and ethyl acetate were added thereto and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and purified by silica gel column chromatography (methylene chloride/ethanol system) followed by conversion into a hydrochloride in a conventional manner. Thus the hydrochloride (220 mg) of the title compound was obtained as a white powder (yield: 35%).

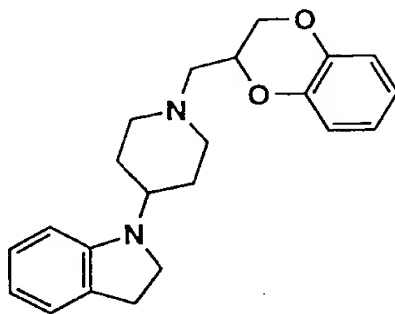
m.p. (hydrochloride): 245°C (decomp.).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.00(3H, d, J=7Hz), 1.82-1.91(2H, m), 2.01-2.13(2H, m), 2.55-2.63(1H, m), 2.88(2H, t, J=8Hz), 3.17-3.28(4H, m), 3.43-3.61(4H, m), 3.71(3H, s), 3.74(3H, s), 3.76-3.83(1H, m), 6.52-6.56(2H, m), 6.75-6.78(1H, m), 6.87-6.90(2H, m), 6.98-7.03(2H, m), 9.90(1H, br-s).

FAB-Mass: 381(MH+).

Example 77: Synthesis of 1-{1-[(1,4-benzodioxan-2-yl)methyl]piperidin-4-yl}indoline



1-(4-Piperidyl)indoline (303 mg) and 2-bromoethyl-1,4-benzodioxane (344 mg) were treated as in Example 2 to give the hydrochloride (372 mg) of the title compound as beige crystals (yield: 67%).

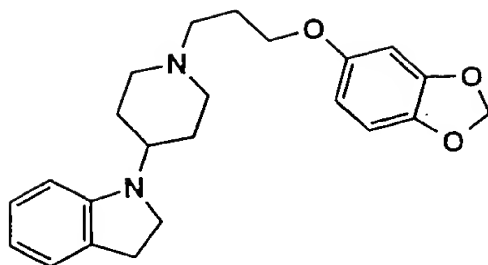
m.p. (hydrochloride): 200 - 205°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.88(2H, d, J=12.4Hz), 2.10-2.25(2H, m), 2.92(2H, t, J=8.4Hz), 3.13-3.58(7H, m), 3.72-3.82(2H, m), 4.05(1H, dd, J=11.4Hz, 6.8Hz), 4.34(1H, dd, J=11.4Hz, 2Hz), 4.90-4.95(1H, m), 6.67(1H, d, J=6.8Hz), 6.68(1H, dd, J=6.8Hz, 6.6Hz), 6.84-6.96(4H, m), 7.04(1H, dd, J=9Hz, 7.6Hz), 7.08(1H, d, J=7.6Hz), 11.40(1H, br-s).

ESI-Mass: 351(MH+).

Example 78: Synthesis of 1-{1-[3-(3,4-methylenedioxypropyl)piperidin-4-yl]indoline



1-(4-Piperidyl)indoline (303 mg) and 3-bromopropoxy-1,2-methylenedioxybenzene (389 mg) were treated as in Example 2 to give the hydrochloride (443 mg) of the title compound as pale blue crystals (yield: 73%).

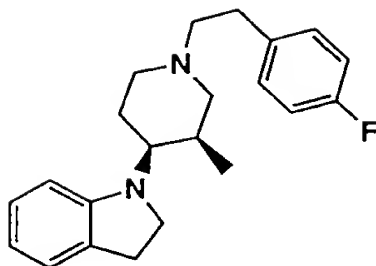
m.p. (hydrochloride): 210 - 212°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.84(2H, d, J=11.6Hz), 1.98-2.18(4H, m), 2.88(2H, t, J=8.4Hz), 3.05(2H, q, J=11.6Hz), 3.11-3.20(2H, m), 3.30(2H, t, J=8.4Hz), 3.57(2H, d, J=11.6Hz), 3.72(1H, m), 3.97(2H, t, J=6Hz), 5.94(2H, s), 6.37(1H, dd, J=8.4Hz, 2.8Hz), 6.54(1H, d, J=7.6Hz), 6.57(1H, t, J=7.6Hz), 6.63(1H, d, J=2.8Hz), 6.80(1H, d, J=8.4Hz), 6.99(1H, t, J=7.6Hz), 7.02(1H, d, J=7.6Hz), 10.45(1H, br-s).

ESI-Mass: 381(MH⁺).

Example 79: Synthesis of cis-1-[1-(4-fluorophenethyl)-3-methylpiperidin-4-yl]indoline



Indoline (238 mg), 1-[2-(4-fluorophenyl)ethyl]-3-methyl-4-piperidone (588 mg) obtained in Production Example 40-5 and triacetoxylated sodium borohydride (1.19 g) were treated as in Example 101 to give the title compound (100 mg) as a yellow oil (yield: 15%).

m.p. (oxalate): 229 - 230°C.

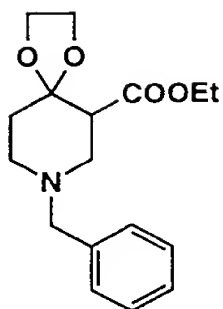
$^1\text{H-NMR}$ (400 MHz, CDCl_3):

δ (ppm) 1.09(3H, d, $J=6.5\text{Hz}$), 1.69(1H, m), 2.10(2H, m), 2.26(1H, br-d), 2.30(1H, m), 2.47(1H, m), 2.56(1H, m), 2.74(2H, m), 2.81(1H, br-d), 2.98(3H, m), 3.42(1H, m), 3.56(1H, q, $J=9.0\text{Hz}$), 3.64(1H, m), 6.31(1H, br-d), 6.54(1H, br-t), 6.96(2H, br-d), 7.03(2H, m), 7.17(2H, m).

FAB-Mass: 339(MH+).

Example 80-1: Synthesis of 1-benzyl-3-hydroxymethyl-4-piperidone

(80-1-1) Ethyl 1-benzyl-4,4-ethylenedioxy-3-piperidinecarboxylate

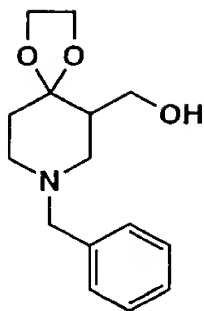


p-Toluenesulfonic acid monohydrate (1.5 g) was added to a solution (600 ml) of ethyl 1-benzyl-4-oxo-3-piperidinecarboxylate (CAS Registry No. 1454-53-1, 44.7 g) and ethylene glycol (100 ml) in toluene and the resultant mixture was heated under reflux overnight. After cooling the mixture to room temperature, ice water (500 ml) and a saturated aqueous solution (300 ml) of sodium bicarbonate were added thereto followed by extraction with ethyl acetate (400 ml) for three times. The organic phase was washed successively with water (200 ml) twice and brine (300 ml) and dried over anhydrous magnesium sulfate. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (30.4 g) as a yellow oil (yield: 66%).

$^1\text{H-NMR}$ (400 MHz, CDCl_3):

$\delta(\text{ppm})$ 1.22(3H, t, $J=6.0\text{Hz}$), 1.74(1H, m), 1.98(1H, m), 2.48(1H, m), 2.68(2H, m), 2.82(2H, m), 3.49(1H, d, $J=11.0\text{Hz}$), 3.57(1H, d, $J=11.0\text{Hz}$), 3.89(1H, d, $J=7.0\text{Hz}$), 3.96(3H, m), 4.13(2H, q, $J=6.0\text{Hz}$), 7.22-7.32(5H, m).

(80-1-2) 1-Benzyl-4,4-ethylenedioxy-3-piperidinemethanol

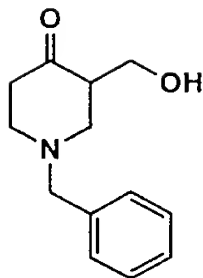


In a stream of nitrogen, lithium aluminum hydride (702 mg) was carefully added to ice cooled dry tetrahydrofuran (100 ml). Into the resultant mixture was slowly added dropwise a solution of ethyl 1-benzyl-4,4-ethylenedioxy-3-piperidinecarboxylate (4.58 g) obtained above in tetrahydrofuran (30 ml). The resultant mixture was gradually heated and further stirred at room temperature overnight. Under ice cooling, water (0.7 ml), a 5 N aqueous solution (2.1 ml) of sodium hydroxide and further water (2.1 ml) were successively added to the reaction mixture carefully. Next, the resulting mixture was dried over anhydrous sodium sulfate and filtered through celite followed by concentration under reduced pressure. Thus the title compound (4.03 g) was obtained as a colorless oil (yield: 100%).

$^1\text{H-NMR}$ (400 MHz, CDCl_3):

δ (ppm) 1.67(1H, m), 1.92(1H, m), 2.01(1H, m), 2.43-2.66(3H, m), 2.70(1H, br-d), 3.49(2H, s), 3.77(1H, d, $J=11.0\text{Hz}$), 3.83(1H, d, $J=11.0\text{Hz}$), 3.96(4H, br-s), 7.23-7.33(5H, m).

(80-1-3) 1-Benzyl-3-hydroxymethyl-4-piperidone

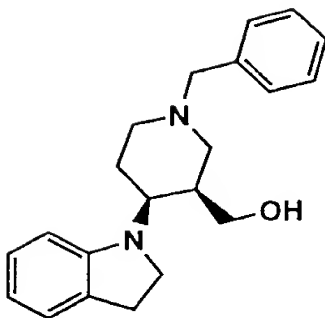


1-Benzyl-4,4-ethylenedioxy-3-piperidinemethanol (960 mg) was dissolved under ice cooling in a mixed solvent of water (10 ml) and conc. sulfuric acid (6 ml). The resultant mixture was gradually heated to room temperature and further stirred for a day. Under ice cooling, a 5 N aqueous solution of sodium hydroxide was added to the mixture to adjust to ca. pH 8. After extracting with chloroform (50 ml) twice, the mixture was washed successively with water and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound (710 mg) as a colorless oil (yield: 89%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 2.47(2H, m), 2.60(2H, m), 2.70(1H, m), 3.01(2H, m), 3.62(2H, s), 3.71(1H, dd, J=7.5Hz, 13.5Hz), 3.76(1H, br-d), 7.25-7.37(5H, m).

Example 80-2: Synthesis of cis-1-(1-benzyl-3-hydroxymethylpiperidin-4-yl)indoline



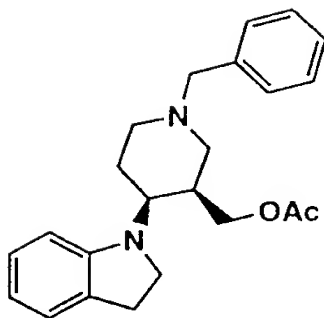
Indoline (238 mg), 1-benzyl-3-hydroxymethyl-4-piperidone (548 mg) and triacetoxyated sodium borohydride (1.19 g) were treated as in Example 1 to give the title compound (140 mg) as a yellow powder (yield: 22%).

$^1\text{H-NMR}$ (400 MHz, CDCl_3):

δ (ppm) 1.79(1H, br-d), 2.08(1H, br-s), 2.14(1H, dt, $J=2.8\text{Hz}$, 12.0Hz), 2.49(1H, br-d), 2.54(1H, dt, $J=4.5\text{Hz}$, 12.0Hz), 3.02(3H, m), 3.14(1H, br-d), 3.49(1H, d, $J=12.0\text{Hz}$), 3.55(1H, d, $J=12.0\text{Hz}$), 3.56(1H, t, $J=12.5\text{Hz}$), 3.64(1H, q, $J=9.0\text{Hz}$), 3.82(2H, m), 3.97(1H, br-d), 6.28(1H, d, $J=7.5\text{Hz}$), 6.56(1H, t, $J=7.5\text{Hz}$), 7.00(1H, t, $J=7.5\text{Hz}$), 7.04(1H, d, $J=7.5\text{Hz}$), 7.27-7.37(5H, m).

Example 81-1: Synthesis of cis-1-(3-acetoxymethylpiperidin-4-yl)indoline

(81-1-1) cis-1-(1-Benzyl-3-acetoxymethylpiperidin-4-yl)-indoline

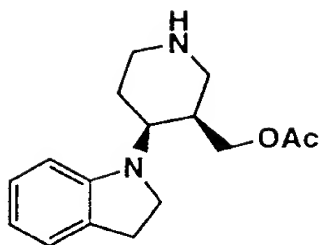


Under ice cooling, triethylamine (111 mg) and acetyl chloride (86 mg) were added to a solution of cis-1-(1-benzyl-3-hydroxymethylpiperidin-4-yl)indoline (322 mg) in tetrahydrofuran (3 ml). The resultant mixture was stirred under ice cooling for 30 min and then at room temperature for additional 1 hr. Then ethyl acetate (15 ml) was added thereto followed by filtration through celite. After removing the solvent under reduced pressure, the residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (340 mg) as a yellow oil (yield: 93%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.76(1H, br-d), 1.83(3H, s), 1.99-2.20(3H, m), 2.44(1H, m), 2.92-3.03(4H, m), 3.40(1H, d, J=13.0Hz), 3.48-3.56(3H, m), 3.58(1H, d, J=13.0Hz), 4.13(1H, dd, J=4.2Hz, 10.0Hz), 4.63(1H, t, J=10.0Hz), 6.31(1H, d, J=7.5Hz), 6.57(1H, t, J=7.5Hz), 7.02(2H, m), 7.21-7.31(5H, m).

(81-1-2) cis-1-(3-Acetoxymethylpiperidin-4-yl)indoline



Under ice cooling, a solution of 1-chloroethyl chloroformate (135 mg) in dichloroethane (1 ml) was added to a solution of cis-1-(1-benzyl-3-acetoxymethylpiperidin-4-yl)indoline (340 mg) in dichloroethane (5 ml). After stirring for 30 min, the mixture was heated under reflux for 1 hr. Then, it was cooled and concentrated under reduced pressure. After adding methanol (10 ml) thereto, the mixture was stirred at 50°C for 10 min and heated under reflux for 30 min. Then it was cooled to room temperature again and concentrated under reduced pressure. After adding a saturated aqueous solution (10 ml) of sodium bicarbonate, the mixture was extracted with chloroform (15 ml) for three times. The organic phase was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound (290 mg) as a yellow powder (yield: 100%).

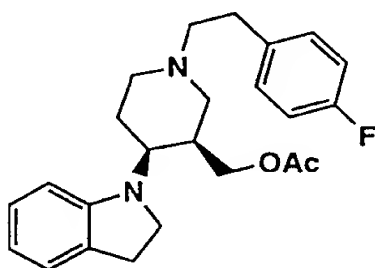
¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.94(1H, dd, J=4.5Hz, 13.0Hz), 1.99(3H, s), 2.45(1H, m), 2.79(1H, dt, J=3.0Hz, 12.0Hz), 2.87(1H, dd, J=3.0Hz, 12.5Hz), 2.97(3H, m), 3.19(1H, br-d), 3.26(1H, br-d, J=13.5Hz), 3.55(2H, t, J=9.0Hz), 3.64(1H, td, J=5.0Hz, 12.5Hz), 4.20(1H,

dd, J=4.5Hz, 11.5Hz), 4.56(1H, t, J=10.5Hz), 6.34(1H, d, J=7.5Hz), 6.58(1H, t, J=7.5Hz), 7.03(2H, m).

Example 81-2 Synthesis of cis-1-[1-(4-fluorophenethyl)-3-hydroxymethylpiperidin-4-yl]indoline

(81-2-1) cis-1-[1-(4-Fluorophenethyl)-3-acetoxymethylpiperidin-4-yl]indoline

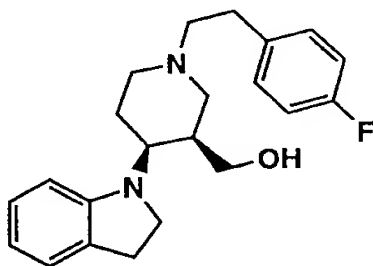


cis-1-(3-Acetoxymethylpiperidin-4-yl)indoline (280 mg) was dissolved in dimethylformamide (4 ml) and methanol (1 ml). To the resultant solution were added triethylamine (222 mg) and 4-fluorophenethyl bromide (285 mg) followed by stirring at 50°C for 2 hr. Then the reaction mixture was cooled and water (50 ml) was added thereto. After extracting with ether (50 ml) twice, the organic phase was washed with water (20 ml) twice and a 2 N aqueous solution (50 ml) of sodium hydroxide once and dried over anhydrous magnesium sulfate. Then the solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (100 mg) as a colorless oil (yield: 28%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.77(1H, br-d), 1.93(3H, s), 1.98(1H, dd, J=4.0Hz, 12.0Hz), 2.12-2.21(2H, m), 2.42-2.63(4H, m), 2.73(2H, m), 2.98(2H, m), 3.06(1H, br-d), 3.46-3.58(3H, m), 4.20(1H, dd, J=3.5Hz, 10.0Hz), 4.46(1H, t, J=9.5Hz), 6.33(1H, d, J=7.5Hz), 6.58(1H, t, J=7.5Hz), 6.96(2H, br-t), 7.04(2H, br-d), 7.15(2H, m).

(81-2-2) cis-1-[1-(4-Fluorophenethyl)-3-hydroxymethylpiperidin-4-yl]indoline



Potassium carbonate (130 mg) was added to a solution of cis-1-[1-(4-fluorophenethyl)-3-acetoxymethylpiperidin-4-yl]indoline (100 mg) obtained above in methanol (6 ml) and the resultant mixture was stirred at room temperature for 4 hr. After adding ether (20 ml), the mixture was filtered through celite and the filtrate was concentrated under reduced pressure. Ethyl acetate (20 ml) was added to the residue followed by filtration again. Then the filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the

title compound (40 mg) as a pale yellow powder (yield: 45%).

m.p. (oxalate): 173 - 174°C.

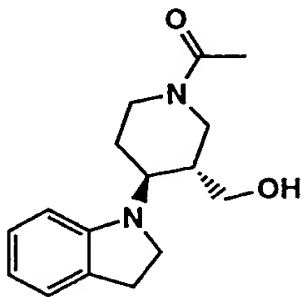
¹H-NMR (400 MHz, CDCl₃):

1.82(1H, br-d), 2.08(1H, br-s), 2.18(1H, t, J=11.0Hz),
2.50(2H, m), 2.59(2H, t, J=7.5Hz), 2.80(2H, br-t), 3.01(2H, m),
3.16(2H, m), 3.57(1H, m), 3.64(1H, q, J=9.0Hz), 3.82(2H, m),
3.94(1H, d, J=10.5Hz), 6.27(1H, d, J=7.5Hz), 6.55(1H, t,
J=7.5Hz), 6.96-7.06(4H, m), 7.14(2H, m).

FAB-Mass: 355(MH+).

Example 82: Synthesis of trans-1-[1-(4-fluorophenethyl)-3-hydroxymethylpiperidin-4-yl]indoline

(82-1) trans-1-(1-Acetyl-3-hydroxymethylpiperidin-4-yl)indoline



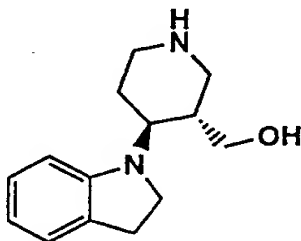
To a solution of trans-1-(1-acetyl-3-ethoxycarbonyl-piperidin-4-yl)indoline (780 mg) in ethanol (40 ml) was added sodium borohydride (5.7 g) in 3 portions at 30min. intervals. After stirring at room temperature overnight, sodium borohydride (3.3 g) was added thereto and the resultant mixture was stirred for additional 4 hr. Then ethyl acetate (20 ml)

and water (50 ml) were successively added carefully to the reaction mixture followed by extraction with ethyl acetate (50 ml) for three times. The organic phase was washed with water (100 ml) twice and brine once, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/methanol system) to give the title compound (250 mg) as a yellow powder (yield: 39%).

$^1\text{H-NMR}$ (400 MHz, CDCl_3):

δ (ppm) 1.60(1H, m), 1.72(1H, m), 1.97(1H, m), 2.11(3H of 1tautomer, s), 2.14(3H of 1tautomer, s), 2.51(2H, m), 2.92-3.15(3H, m), 3.28(1H, m), 3.38-3.81(4H, m), 3.89(1H of 1tautomer, br-d), 3.99(1H of 1tautomer, br-d), 4.75(1H, br-d), 6.50(1H, m), 6.67(1H, m), 7.05(2H, m).

(82-2) trans-1-(3-Hydroxymethylpiperidin-4-yl)indoline



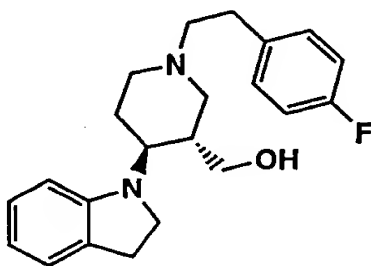
Sodium hydroxide (220 mg) was added to a solution of trans-1-(1-acetyl-3-hydroxymethylpiperidin-4-yl)indoline (250 mg) in ethanol (10 ml)-water (0.5 ml) mixtures and the resultant mixture was heated under reflux for 20 hr. After cooling and adding water (50 ml), the resultant mixture was

extracted with chloroform (30 ml) for three times. The organic phase was washed successively with water (50 ml) and brine (50 ml), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound (190 mg) as a colorless oil (yield: 85%).

$^1\text{H-NMR}$ (400 MHz, CDCl_3):

δ (ppm) 1.56-1.69(2H, m), 1.95-2.07(1H, m), 2.46(1H, t, $J=11.5\text{Hz}$), 2.64(1H, dt, $J=2.5\text{Hz}$, 11.5Hz), 2.95(2H, m), 3.17(2H, m), 3.34(1H, br-q), 3.42(1H, dt, $J=4.5\text{Hz}$, 10.5Hz), 3.50(1H, dt, $J=5.0\text{Hz}$, 8.5Hz), 3.61(1H, dd, $J=5.0\text{Hz}$, 11.0Hz), 3.67(1H, dd, $J=5.0\text{Hz}$, 11.0Hz), 6.53(1H, d, $J=7.5\text{Hz}$), 6.66(1H, t, $J=7.5\text{Hz}$), 7.06(2H, m).

(82-3) trans-1-[1-(4-Fluorophenethyl)-3-hydroxymethylpiperidin-4-yl]indoline



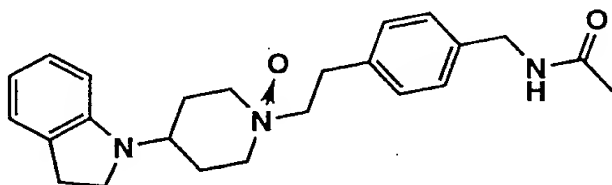
trans-1-(3-Hydroxymethylpiperidin-4-yl)indoline (190 mg) was reacted with triethylamine (152 mg) and 4-fluorophenethyl bromide (406 mg) as in Example 2 to give the title compound (210 mg) as a brown oil (yield: 72%).
m.p. (oxalate): 113 - 116°C.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.69(1H, m), 1.79(1H, m), 1.92(1H, t, J=11.0Hz), 2.07(1H, br-t), 2.17(1H, m), 2.58(2H, br-t), 2.79(2H, br-t), 2.95(2H, m), 3.06(1H, br-d), 3.13(1H, br-d), 3.35(2H, m), 3.49(1H, m), 3.64(1H, dd, J=4.5Hz, 11.0Hz), 3.71(1H, dd, J=6.0Hz, 11.0Hz), 6.52(1H, d, J=7.5Hz), 6.67(1H, t, J=7.5Hz), 6.97(2H, t, J=8.0Hz), 7.07(2H, br-t), 7.15(2H, m).

FAB-Mass: 355(MH⁺).

Example 83: Synthesis of 1-[2-(4-acetamidomethylphenyl)ethyl]-4-(indan-1-yl)piperidin-1-oxide



1-[1-(4-Acetoamidomethylphenethyl)piperidin-4-yl]-indoline (0.50 g) obtained in Example 36 was dissolved in methylene chloride (20 ml) and 70% m-chloroperbenzoic acid (0.37 g) was added thereto at 0°C. The reaction solution was stirred at room temperature for 30 min followed by the addition of sodium carbonate (5.0 g). The reaction mixture was filtered through alumina and washed with a mixture of methylene chloride and methanol (10 : 1). After concentrating the filtrate under reduced pressure, the resulting residue was purified by silica

gel column chromatography (methylene chloride/methanol system) to give the title compound (0.15 g) as a white powder (yield: 28.8%).

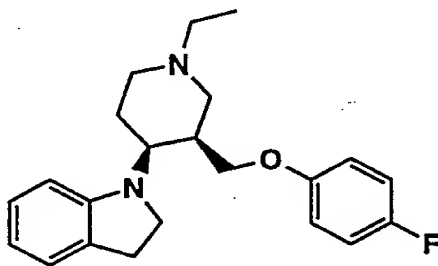
m.p.: 130 - 131°C.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.77(2H, br-d), 2.03(3H, s), 2.50-2.73(5H, m), 2.97(2H, t, J=8.0Hz), 3.16-3.26(3H, m), 3.36-3.60(5H, m), 4.40(2H, d, J=9.6Hz), 6.32(1H, m), 6.41(1H, d, J=8.0Hz), 6.65(1H, t, J=7.6Hz), 7.04(1H, t, J=7.6Hz), 7.08(1H, d, J=7.2Hz), 7.19(2H, d, J=8.0Hz), 7.23(2H, d, J=8.0Hz).

FAB-Mass: 394(MH⁺).

Example 84: Synthesis of cis-1-[1-ethyl-3-(4-fluorophenoxymethyl)piperidin-4-yl]indoline



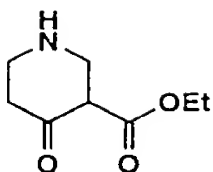
Under a nitrogen gas stream, 4-fluorophenol (168 mg) and triphenylphosphine (420 mg) were added to a solution of cis-1-(1-ethyl-3-hydroxymethylpiperidin-4-yl)indoline (300 mg) in tetrahydrofuran (4 ml). After cooling the resultant mixture to -10°C, diethyl azodicarboxylate (278 mg) was gradually added dropwise thereinto. Then the resultant

mixture was gradually warmed to room temperature and stirred at the same temperature overnight. After adding water (40 ml), the reaction mixture was extracted with ether (40 ml) for three times. The organic phase was washed successively with a saturated aqueous solution (40 ml) of sodium bicarbonate and a 1 N aqueous solution (40 ml) of sodium hydroxide, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Fuji Silysia Chemical Ltd. NH-DM2035, hexane/ethyl acetate system) to give the title compound (100 mg) as a colorless oil (yield: 25%).

m.p. (oxalate): 97 - 98°C.

$\delta(\text{ppm})$ 1.04(3H, t, $J=7.0\text{Hz}$), 1.82(1H, m), 2.00(1H, dq, $J=3.5\text{Hz}$, 11.5Hz), 2.11(2H, m), 2.35(1H, m), 2.44(1H, m), 2.62(1H, m), 2.98(3H, m), 3.17(1H, br-d, $JJ=10.5\text{Hz}$), 3.54(3H, m), 4.10(1H, dd, $J=3.5\text{Hz}$, 8.0Hz), 4.34(1H, t, $J=8.5\text{Hz}$), 6.38(1H, d, $J=7.5\text{Hz}$), 6.59(1H, t, $J=7.5\text{Hz}$), 6.77(2H, m), 6.88(2H, br-t), 7.01-7.06(2H, m).

Example 85-1: Synthesis of ethyl 1-acetyl-4-oxo-3-
piperidinecarboxylate

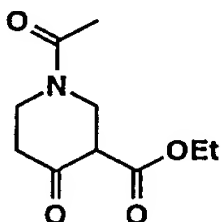


10% palladium/active carbon (2 g) was added to a solution of ethyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride (30 g) in methanol (500 ml) and the resultant mixture was stirred at room temperature under hydrogen atmosphere for a day. After filtering the reaction mixture through celite, the filtrate was concentrated under reduced pressure to give the title compound (20.0 g) as a white powder (yield: 97%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.30(3H, t, J=6.0Hz), 2.66(2H, t, J=5.5Hz), 3.42(2H, t, J=5.5Hz), 3.84(2H, s), 4.29(2H, q, J=6.0Hz).

(85-1-2) Ethyl 1-acetyl-4-oxo-3-piperidinecarboxylate



Ethyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride (20.0 g) obtained above was dissolved in pyridine (150 ml). To the resultant solution was added acetic anhydride (10.2 g) at room temperature over 5 min or longer and the resultant mixture was stirred at room temperature for 2 hr.

After adding ethyl acetate (500 ml), the reaction mixture was filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate/methanol system) to give the title compound (19.9 g) as a white powder (yield: 97%).

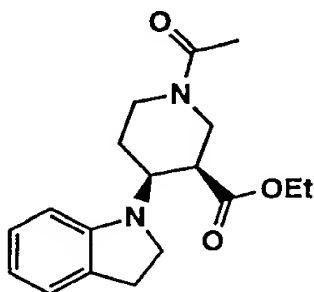
¹H-NMR (400 MHz, CDCl₃):

δ(ppm) mixture of tautomers

major: 1.34(3H, t, J=6.0Hz), 2.16(3H, s), 2.39(2H, t, J=5.5Hz), 3.75(2H, t, J=5.5Hz), 4.10(2H, s), 4.28(2H, q, J=6.0Hz), 12.08(1H, s).

minor: 1.32(3H, t, J=6.0Hz), 2.15(3H, s), 2.44(2H, t, J=5.5Hz), 3.60(2H, t, J=5.5Hz), 4.23(2H, s), 4.26(2H, q, J=6.0Hz), 12.06(1H, s).

Example 85-2: Synthesis of cis-1-(1-acetyl-3-ethoxycarbonylpiperidin-4-yl)indoline

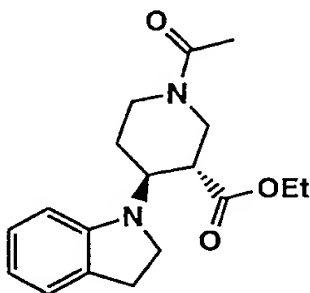


Indoline (12.5 g), ethyl 1-acetyl-4-oxo-3-piperidinecarboxylate (22.3 g) and triacetoxylated sodium borohydride (48.7 g) were treated as in Example 1 to give the title compound (7.12 g) as a pale yellow powder (yield: 22%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) mixture of tautomers 1.19(3H of 1tautomer, t, J=6.0Hz), 1.21(3H of 1tautomer, t, J=6.0Hz), 2.07(3H of 1tautomer, s), 2.14(3H of 1tautomer, s), 2.36-3.07(5H, m), 3.19-3.62(3H, m), 3.75(1H of 1tautomer, m), 3.93-4.13(3H, m), 4.66(1H of 1tautomer, br-d), 4.82(1H of 1tautomer, br-d), 6.34(1H, d, J=7.5Hz), 6.61(1H, t, J=7.5Hz), 7.05(2H, m).

Example 85-3: Synthesis of trans-1-(1-acetyl-3-ethoxycarbonylpiperidin-4-yl)indoline

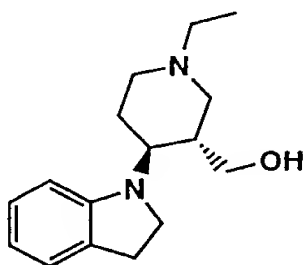


Potassium carbonate (138 mg) was added to a solution (150 ml) of cis-1-(1-acetyl-3-ethoxycarbonylpiperidin-4-yl)indoline (4.35 g) in ethanol and the resultant mixture was stirred at 60°C for a day followed by concentration under reduced pressure. Ethyl acetate (200 ml) was added to the residue, which was then washed successively with water (50 ml) once and brine (50 ml) once, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Thus the title compound (4.22 g) was obtained as a yellow oil (yield: 97%).

¹H-NMR (400 MHz, CDCl₃):

[illegible]

(85-4-1) trans-1-(1-Ethyl-3-hydroxymethylpiperidin-4-yl)indoline



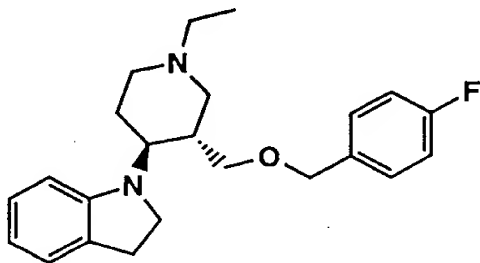
- 265 -

the resultant mixture to room temperature, ethyl acetate (30 ml) was added thereto followed by drying over anhydrous sodium sulfate. After filtering and concentrating under reduced pressure, the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system) to give the title compound (340 mg) as a pale yellow powder (yield: 49%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.11(3H, t, J=6.0Hz), 1.68(1H, m), 1.79(2H, m), 1.96(1H, dt, J=2.5Hz, 11.0Hz), 2.17(1H, m), 2.44(2H, q, J=6.0Hz), 2.95(2H, m), 3.05(2H, m), 3.34(2H, m), 3.48(1H, dt, J=5.0Hz, 8.0Hz), 3.63(1H, dd, J=5.0Hz, 10.0Hz), 3.69(1H, dd, J=5.5Hz, 10.5Hz), 6.51(1H, d, J=7.5Hz), 6.65(1H, t, J=7.5Hz), 7.06(2H, m).

(85-4-2) trans-1-[1-Ethyl-3-(4-fluorobenzyloxymethyl)piperidin-4-yl]indoline



To a suspension of 55% sodium hydride (83 mg) in dimethylformamide (3 ml) were added under ice cooling a solution of trans-1-(1-ethyl-3-hydroxymethylpiperidin-4-yl)indoline

(340 mg) in dimethylformamide (2 ml) and 4-fluorobenzyl bromide (378 mg). The resulting mixture was gradually warmed to room temperature and then stirred at the same temperature overnight. After adding water (50 ml), it was extracted with ethyl acetate (50 ml) thrice. The organic phase was washed with water (50 ml) once and then with brine (50 ml) once, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Next, the residue was purified by silica gel column chromatography (Fuji Silysia Chemical Ltd. NH-DM2035, hexane/ethyl acetate system) to give the title compound (50 mg) as a colorless oil (yield: 10%).

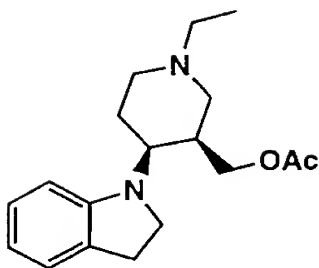
m.p. (oxalate): 177 - 178°C.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.11(3H, t, J=6.0Hz), 1.73(1H, m), 1.96(2H, m), 2.15(1H, m), 2.45(2H, q, J=6.0Hz), 2.83-2.97(2H, m), 3.04(1H, m), 3.23(1H, br-d), 3.32(3H, m), 3.57(1H, dd, J=2.5Hz, 9.0Hz), 4.35(1H, d, J=11.5Hz), 4.41(1H, d, J=11.5Hz), 4.50(2H, s), 6.37(1H, d, J=7.5Hz), 6.57(1H, t, J=7.5Hz), 6.95(2H, br-t), 7.02(2H, m), 7.22(2H, dd, J=6.0Hz, 9.0Hz).

FAB-Mass: 369(MH⁺).

Example 86: Synthesis of cis-1-[1-ethyl-3-(4-fluorobenzoyloxymethyl)piperidin-4-yl]indoline
(86-1) cis-1-(1-Ethyl-3-acetoxymethylpiperidin-4-yl)indoline



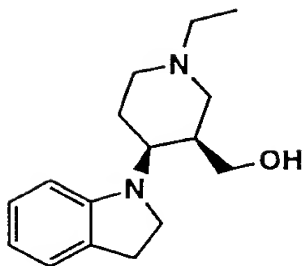
Triethylamine (1.21 g) and ethyl iodide (1.72 g) were added to a solution of cis-1-(3-acetoxymethylpiperidin-4-yl)indoline (3.53 g) in dimethylformamide (40 ml) followed by stirring the mixture at 50°C for 4 hr. Under ice cooling, water (150 ml) was added to the reaction mixture, which was then extracted with ethyl acetate (100 ml) for three times. The organic phase was washed with water (50 ml) twice and brine (100 ml) once, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol system) to give the title compound (2.06 g) as a pale yellow oil (yield: 63%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.04(3H, t, J=7.0Hz), 1.77(1H, m), 1.92(3H, s), 1.96-2.11(3H, m), 2.31-2.48(3H, m), 2.93-3.03(4H, m), 3.49(1H, m), 3.56(2H, m), 4.22(1H, dd, J=4.5Hz, 10.5Hz), 4.47(1H, dd, J=9.0Hz, 10.0Hz), 6.32(1H, d, J=7.5Hz), 6.56(1H, t, J=7.5Hz), 7.02(2H, m).

(86-2) cis-1-(1-Ethyl-3-hydroxymethylpiperidin-4-

yl)indoline

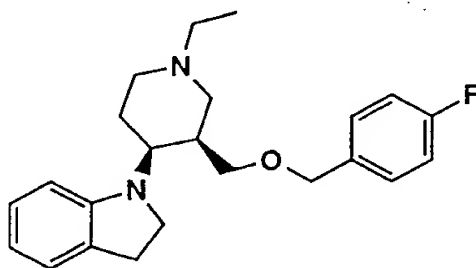


Potassium carbonate (3.0 g) was added to a solution of cis-1-(1-ethyl-3-acetoxymethylpiperidin-4-yl)indoline (2.06 g) in methanol (120 ml) and the resultant mixture was stirred at room temperature for 4 hr. After adding ether (80 ml), the mixture was filtered through celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Fuji Silysia Chemical Ltd. NH-DM2035, hexane/ethyl acetate system) to give the title compound (1.19 g) as a pale yellow powder (yield: 67%).

$^1\text{H-NMR}$ (400 MHz, CDCl_3):

δ (ppm) 1.11(3H, t, $J=7.0\text{Hz}$), 1.82(1H, br-d), 2.06(1H, m), 2.11(1H, dd, $J=3.0\text{Hz}$, 11.5Hz), 2.40(2H, q, $J=7.0\text{Hz}$), 2.41(1H, m), 2.52(1H, m), 3.01(2H, m), 3.10(1H, m), 3.16(1H, td, $J=2.0\text{Hz}$, 11.5Hz), 3.56(1H, td, $J=5.0\text{Hz}$, 12.0Hz), 3.66(1H, q, $J=9.0\text{Hz}$), 3.82(1H, dd, $J=6.0\text{Hz}$, 9.0Hz), 3.87(1H, br-d), 3.98(1H, td, $J=2.0\text{Hz}$, 11.5Hz), 6.27(1H, d, $J=7.5\text{Hz}$), 6.55(1H, t, $J=7.5\text{Hz}$), 7.00(1H, br-t), 7.04(1H, br-d).

(86-3) cis-1-[1-Ethyl-3-(4-

[illegible]

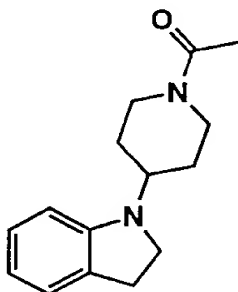
$\delta(\text{ppm})$ 1.07(3H, t, $J=7.0\text{Hz}$), 1.75(1H, m), 1.94(1H, m), 2.07(1H, m), 2.31-2.54(3H, m), 2.94(3H, m), 3.15(1H, br-d), 3.48(2H, m), 3.62(1H, dd, $J=4.0\text{Hz}$, 8.0Hz), 3.86(1H, m), 4.18(1H,

d, J=4.0Hz), 4.41(1H, d, J=4.0Hz), 6.36(1H, d, J=7.5Hz), 6.57(1H, t, J=7.5Hz), 6.95(2H, br-t), 7.00-7.06(2H, m), 7.20(2H, dd, J=6.0Hz, 9.0Hz).

FAB-Mass: 369(MH+).

Example 87: Synthesis of 1-(1-acetylpiperidin-4-yl)indoline-7-carbaldehyde

(87-1) 1-(1-Acetylpiperidin-4-yl)indoline



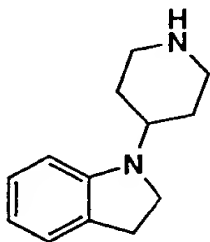
Indoline (25 ml), 1-acetyl-4-piperidone (25 g) and glacial acetic acid (20 ml) were dissolved in methanol (300 ml). After adding 10% palladium carbon (1.0 g) thereto, catalytic reduction was carried out under atmospheric pressure. After the completion of the reaction, the reaction solution was filtered through celite, washed with methanol and concentrated under reduced pressure. The residue was partitioned between water and ethyl acetate and basified with a 5 N aqueous solution of sodium hydroxide followed by extraction with ethyl acetate. The ethyl acetate layer was washed with water and brine, dried and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl

acetate/hexane system) to give the title compound (35.6 g) as a pale yellow wax (yield: 82.2%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.50-1.62(2H, m), 1.81-1.93(2H, m), 2.12(3H, s), 2.59(1H, br-t), 2.96(2H, t, J=7.2Hz), 3.15(1H, br-t), 3.31-3.39(2H, m), 3.57-3.64(1H, m), 3.93(1H, br-d), 4.78(1H, br-d), 6.42(1H, d, J=8.0Hz), 6.62(1H, t, J=8.0Hz), 7.02-7.09(2H, m).

(87-2) 1-(4-Piperidin-1-yl)indoline

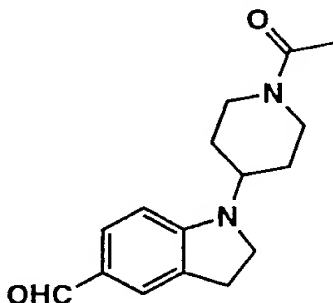


1-(1-Acetylpiperidin-4-yl)indoline (24.4 g) obtained in the above (87-1) was dissolved in ethanol (500 ml). To the resultant solution was added a 5 N aqueous solution (80 ml) of sodium hydroxide followed by heating under reflux for 5 hr. Then the reaction solution was concentrated under reduced pressure and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with brine, dried and concentrated under reduced pressure. The residue was purified by NH-silica gel column chromatography (ethyl acetate) to give the title compound (15.9 g) as a flesh-colored wax (yield: 78.7%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.53-1.65(2H, m), 1.77-1.85(2H, m), 2.68(2H, br-t), 2.95(2H, t, J=7.2Hz), 3.16-3.22(1H, m), 3.39(2H, t, J=7.2Hz), 3.40-3.50(1H, m), 6.41(1H, d, J=8.0Hz), 6.59(1H, t, J=8.0Hz), 7.01-7.07(2H, m).

(87-3) 1-(1-Acetylpiperidin-4-yl)indoline-7-carbaldehyde



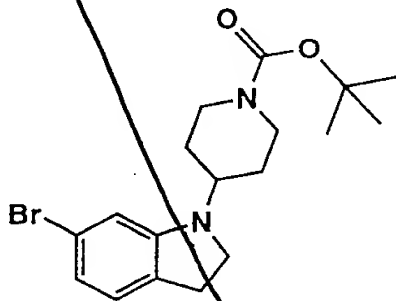
Phosphorus oxychloride (4.60 g) was added dropwise into ice cooled DMF (40 ml) followed by stirring for 15 min. Next, 1-(1-acetylpiperidin-4-yl)indoline (7.32 g) obtained in the above (87-1) was added thereto. The reaction solution was heated at 80°C for 3 hr with vigorous stirring. After cooling, the reaction solution was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with water and brine, dried and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate) to give the title compound (3.2 g) as a pale yellow oil (yield: 39.0%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.62(2H, br-q), 1.81-1.92(2H, m), 2.12(3H, s),

2.61(1H, br-t), 3.04(2H, t, J=7.2Hz), 3.16(1H, br-t), 3.50-3.60(2H, m), 3.66-3.75(1H, m), 3.95(1H, br-d), 4.81(1H, br-d), 6.40(1H, d, J=8.0Hz), 7.53-7.59(2H, m), 9.66(1H, s).

Sub A12
Example 88: Synthesis of 1-[1-(4-t-butoxycarbonyl)piperidin-4-yl]-6-bromoindoline

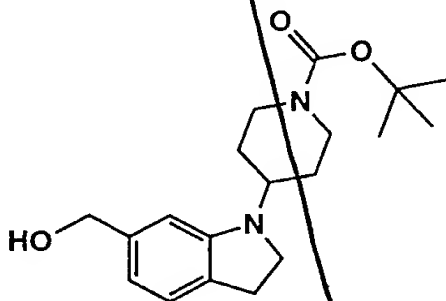


Sub A13
Triacetoxylated sodium borohydride (11.7 g) was added to a mixture of 6-bromoindoline (8.3 g), 1-(4-t-butoxycarbonyl)-4-piperidone (10 g, [CAS Registry No. 7909-07-3]), acetic acid (14.9 g) and dichloroethane (200 ml) followed by stirring overnight. Then the reaction solution was concentrated under reduced pressure, and the pH value thereof was adjusted to 9 with ethyl acetate, an 8 N aqueous solution of sodium hydroxide and water and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (10.3 g) (yield: 64%).

¹H-NMR (400 MHz, CDCl₃):

δ (ppm) 1.48(9H, s), 1.50-1.62(2H, m), 1.75-1.82(2H, m), 2.71-2.82(2H, m), 2.90(2H, t, J=8Hz), 3.40-3.50(1H, m), 3.42(2H, t, J=8Hz), 4.17-4.32(2H, m), 6.52(1H, br-s), 6.75(1H, d, J=8Hz), 6.90(1H, d, J=8Hz).

Example 89: Synthesis of 1-[1-(4-t-butoxycarbonyl)piperidin-4-yl]-6-hydroxymethylindoline



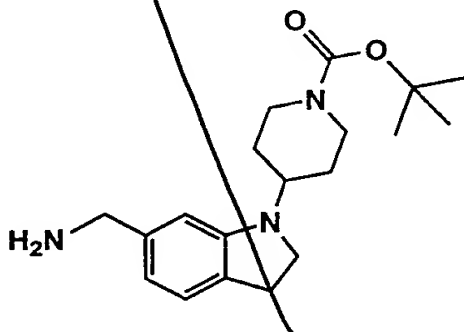
A 2.5 M solution (16 ml) of n-butyllithium in hexane was added dropwise at -78°C into a solution of 1-[1-(4-t-butoxycarbonyl)piperidin-4-yl]-6-bromoindoline (10 g) in tetrahydrofuran (250 ml) over 5 min. After 10 min, dimethylformamide (3.0 ml) was added and the resultant mixture was allowed to warm to room temperature. Next, a saturated aqueous solution of ammonium chloride and ethyl acetate were added thereto and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. To the residue were added ethanol (50 ml) and sodium borohydride (1.0 g) and the resultant mixture was stirred at room temperature for 30 min. Then ice water and ethyl acetate were added to the reaction

1A15
solution and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (7.9 g) (yield: 91%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.48(9H, s), 1.50-1.63(2H, m), 1.75-1.83(2H, m), 2.71-2.83(2H, m), 2.91(2H, t, J=8Hz), 3.39(2H, t, J=8Hz), 3.50-3.60(1H, m), 4.10-4.29(2H, m), 4.31(2H, d, J=6Hz), 6.49(1H, br-s), 6.61(1H, d, J=8Hz), 7.03(1H, d, J=8Hz).

July 4
1A16
Example 90: Synthesis of 1-[1-(4-t-butoxycarbonyl)piperidin-4-yl]-6-aminomethylindoline



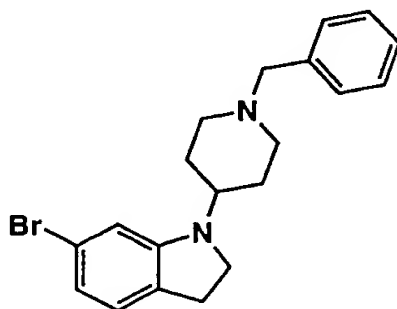
July 4
1A17
Under ice cooling, a solution of diethyl azodicarboxylate (4.6 g) in tetrahydrofuran (20 ml) was added dropwise into a solution of 1-[1-(4-t-butoxycarbonyl)piperidin-4-yl]-6-hydroxymethylindoline (7.9 g), triphenylphosphine (6.9 g) and phthalimide (3.9 g) in tetrahydrofuran (250 ml) and the resultant mixture was stirred at room temperature for 3 hr. After concentrating under reduced pressure, the resulting

A17 residue was purified by silica gel column chromatography (ethyl acetate/hexane system). Then hydrazine hydrate (3.6 g) and ethanol (150 ml) were added thereto followed by heating under reflux for 2 hr. After ice cooling, the resulting crystalline precipitates were filtered off and the filtrate was concentrated under reduced pressure to give the title compound (8.3 g).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.48(9H, s), 1.50-1.60(2H, m), 1.71-1.81(2H, m), 2.72-2.89(2H, m), 2.91(2H, t, J=8Hz), 3.35(2H, t, J=8Hz), 3.49-3.60(1H, m), 3.83(2H, s), 4.13-4.29(2H, m), 6.42(1H, br-s), 6.58(1H, d, J=8Hz), 7.00(1H, d, J=8Hz).

Example 91: Synthesis of 1-(1-benzylpiperidin-4-yl)-6-bromoindoline



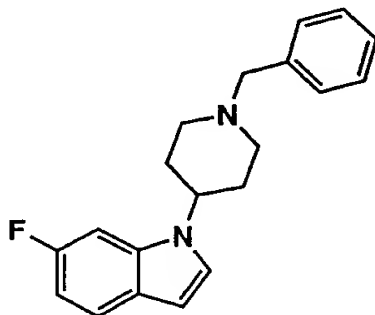
Triacetoxylated sodium borohydride (14.6 g) was added to a mixture of 6-bromoindoline (10 g), 1-benzyl-4-piperidone (9.5 g), acetic acid (12 g) and dichloroethane (200 ml) over 5 min followed by stirring overnight. Then the reaction solution was concentrated under reduced pressure, the pH value thereof was

adjusted to 10 by dilution with ethyl acetate, an 8 N aqueous solution of sodium hydroxide and water and the organic layer was separated. The organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (16.3 g) as a brown oil (yield: 87%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.51-1.60(2H, m), 1.69-1.79(2H, m), 2.01-2.13(2H, m), 2.89(2H, t, J=8Hz), 2.95-3.03(2H, m), 3.22-3.32(1H, m), 3.40(2H, t, J=8Hz), 3.53(2H, s), 6.44(1H, s), 6.65(1H, t, J=8Hz), 6.84(1H, t, J=8Hz), 7.22-7.36(5H, m).

Example 92-1: Synthesis of 1-(1-benzylpiperidin-4-yl)-6-fluoroindole



A solution of 1-benzyl-4-(3-fluorophenyl)-aminopiperidine (11.7 g) synthesized in accordance with the method of Referential Example 1 of JP-B 40-6347 and oxalyl chloride (10.5 g) in ether (300 ml) was heated under reflux for

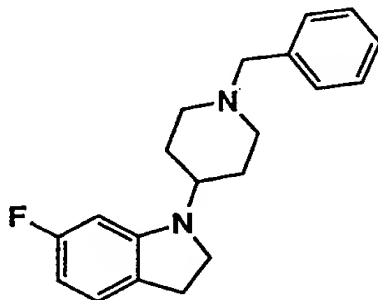
2 hr. After concentrating under reduced pressure, the residue was diluted with methylene chloride (120 ml) and the resultant solution was added dropwise at 0°C into a solution of anhydrous aluminum chloride (27 g) in methylene chloride (100 ml). After stirring for 1 hr, the reaction solution was carefully added to a saturated aqueous solution of sodium bicarbonate. The resulting crystalline precipitates were filtered off and washed with methylene chloride. Next, the filtrate was partitioned between two liquid layers. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system) followed by dilution with tetrahydrofuran (200 ml). Into the resultant solution was added dropwise under ice cooling a 1 M solution (120 ml) of a borane/tetrahydrofuran complex in tetrahydrofuran and the resultant mixture was stirred at room temperature overnight followed by heating under reflux for 3 hr. A saturated aqueous solution of sodium bicarbonate was carefully added dropwise into the reaction solution, then ethyl acetate was added thereto and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was diluted with pyridine (100 ml) and stirred at room temperature for 4 hr. Then a saturated aqueous solution of

sodium bicarbonate and ethyl acetate were added thereto and the layers were separated. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The resulting residue was then purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (3.5 g) as a yellow oil (yield: 35%).

$^1\text{H-NMR}$ (400 MHz, CDCl_3):

δ (ppm) 2.00-2.30(6H, m), 3.02-3.18(2H, m), 3.55-3.67(2H, m), 4.09-4.19(1H, m), 6.49(1H, s), 6.81-6.89(1H, m), 7.00-7.04(1H, m), 7.20(1H, s), 7.22-7.40(5H, m), 7.49-7.56(1H, m).

Example 92-2: Synthesis of 1-(1-benzylpiperidin-4-yl)-6-fluoroindoline



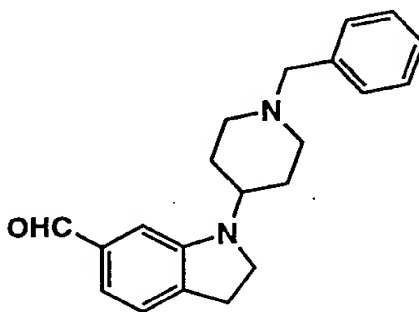
Under ice cooling, a 1 M solution (23 ml) of a borane/tetrahydrofuran complex in tetrahydrofuran was added dropwise into a solution of 1-(1-benzylpiperidin-4-yl)-6-fluoroindole (3.5 g) in trifluoroacetic acid (50 ml) followed by stirring for 2 hr. After adding water thereto, the resultant mixture was concentrated under reduced pressure and then basified by adding ethanol and a 5 N aqueous solution of sodium

hydroxide followed by stirring for 2 hr. Then a saturated aqueous solution of sodium bicarbonate and ethyl acetate were added thereto and the layers were separated. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The residue was then purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (2.0 g) as a brown oil (yield: 57%).

$^1\text{H-NMR}$ (400 MHz, CDCl_3):

δ (ppm) 1.72-1.83(4H, m), 2.89(2H, t, $J=8\text{Hz}$), 3.00-3.09(2H, m), 3.23-3.44(3H, m), 3.42(2H, t, $J=8\text{Hz}$), 3.52-3.61(2H, m), 6.02-6.09(1H, m), 6.20-6.28(1H, m), 6.89-6.93(1H, m), 7.23-7.40(5H, m).

Example 93: Synthesis of 1-(1-benzylpiperidin-4-yl)-6-formylindoline



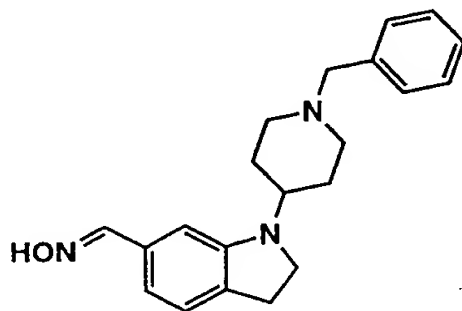
1-(1-Benzylpiperidin-4-yl)-6-bromoindoline (8.54 g) was dissolved in tetrahydrofuran (125 ml). Into the resultant mixture were successively added dropwise in a nitrogen atmosphere a 2.5 M solution (11.5 ml) of n-butyllithium in n-hexane and N,N-dimethylformamide (6.1 ml) followed by

stirring for 2 hr. Then water and ethyl acetate were added thereto and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (6.360 g) as a yellow oil (yield: 86.1%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.74-1.80(4H, m), 2.11(2H, m), 2.99-3.03(2H, m), 3.01(2H, t, J=8.4Hz), 3.43(1H, m), 3.47(2H, t, J=8.4Hz), 3.55(2H, s), 6.82(1H, d, J=1.6Hz), 7.06(1H, dd, J=1.6, 7.2Hz), 7.15(1H, d, J=7.2Hz), 7.28(1H, t, J=4.4Hz), 7.33(1H, d, J=4.4Hz), 9.85(1H, s).

Example 94: Synthesis of 1-(1-benzylpiperidin-4-yl)-6-hydroxyiminomethylindoline



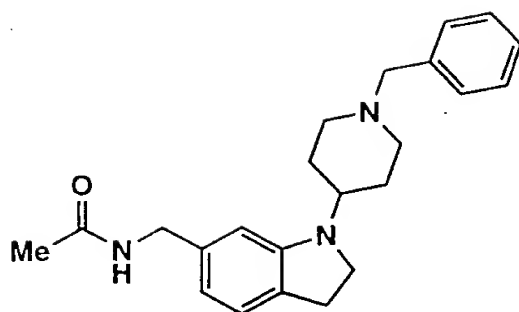
1-(1-Benzylpiperidin-4-yl)-6-formylindoline (6.36 g) was treated as in Example 46 to give the title compound (6.200 g) as a yellow oil (yield: 89.4%).

¹H-NMR (400 MHz, CDCl₃):

Year	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100
1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	

NCC1=CC=C2C(=C1)C(=C3C2CCN3C4CCCCN4Cc5ccccc5) $^1\text{H-NMR}$ (400 MHz, CDCl_3):

Example 96: Synthesis of 1-(1-benzylpiperidin-4-yl)-6-acetamidomethylindoline



1-(1-Benzylpiperidin-4-yl)-6-aminomethylindoline (5.598 g) and acetyl chloride (1.3 ml) were treated as in Example 36 to give the title compound (5.598 g) as a brown oil.

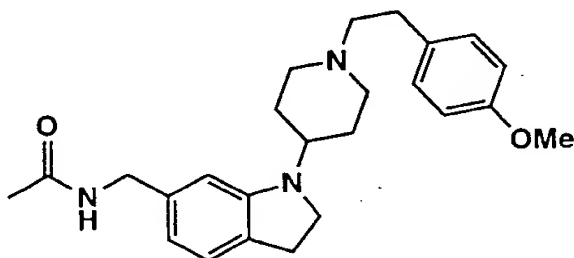
Free

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.76(4H, m), 1.99(3H, s), 2.12(2H, m), 2.91(2H, t, J=8.4Hz), 3.02(2H, br-d), 3.36(1H, m), 3.40(2H, t, J=8.4Hz), 3.57(2H, br-s), 4.31(2H, d, J=5.6Hz), 5.65(1H, m), 6.30(1H, br-d), 6.49(1H, dd, J=1.2, 7.4Hz), 6.98(1H, d, J=7.4Hz), 7.28(1H, m), 7.35(4H, d, J=8.4Hz).

ESI-Mass: 364.1.

Example 97: Synthesis of 1-[1-(4-methoxyphenethyl)piperidin-4-yl]-6-acetamidomethylindoline



1-(Piperidin-4-yl)-6-acetamidomethylindoline (250 mg)

and 4-methoxyphenethyl bromide (240 mg) were treated as in Example 2 to give the title compound (200 mg) as a white powder (yield: 53%).

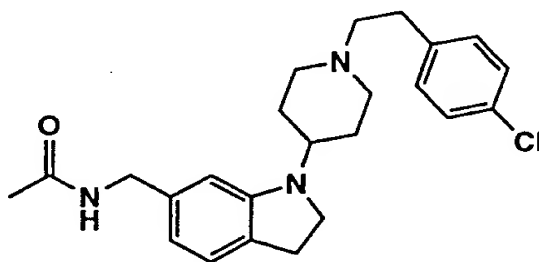
m.p.: 151 - 152°C.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.50-1.63(2H, m), 1.79-1.81(2H, m), 2.01(3H, s), 2.10-2.30(2H, m), 2.75-2.96(4H, m), 2.93(2H, t, J=8Hz), 3.10-3.30(2H, m), 3.36-3.50(1H, m), 3.44(2H, t, J=8Hz), 3.79(3H, s), 4.33(2H, d, J=6Hz), 6.47(1H, s), 6.52(1H, d, J=8Hz), 6.83-6.87(2H, m), 7.00(1H, d, J=8Hz), 7.13-7.16(2H, m).

FAB-Mass: 408(MH+).

Example 98: Synthesis of 1-[1-(4-chlorophenethyl)piperidin-4-yl]-6-acetamidomethylindoline



1-(Piperidin-4-yl)-6-acetamidomethylindoline (250 mg) and 4-chlorophenethyl bromide (240 mg) were treated as in Example 2 to give the title compound (240 mg) as white scaly crystals (yield: 63%).

m.p.: 151 - 152°C.

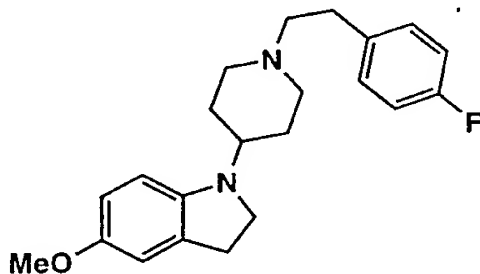
¹H-NMR (400 MHz, CDCl₃):

0364659 050201
T02090 6334960

δ (ppm) 1.50-1.64(2H, m), 1.54-1.90(2H, m), 2.01(3H, s),
2.04-2.34(2H, m), 2.60-3.00(4H, m), 2.93(2H, t, J=8Hz),
3.06-3.26(2H, m), 3.36-3.48(1H, m), 3.43(2H, t, J=8Hz), 4.33(2H,
d, J=6Hz), 6.38(1H, s), 6.51(1H, d, J=8Hz), 7.00(1H, d, J=8Hz),
7.11-7.20(2H, m), 7.23-7.29(2H, m).

FAB-Mass: 412(MH⁺).

Example 99: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-5-methoxyindoline



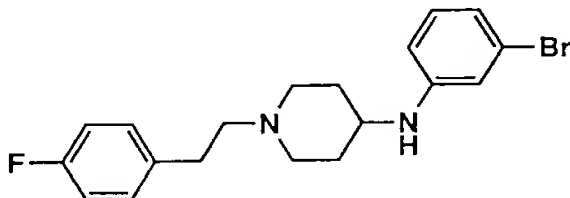
1-(4-Fluorophenethyl)-4-(4-methoxyphenyl)aminopiperidine (10 g) synthesized in accordance with the method of Referential Example 1 of JP-B 40-6347 was treated as in Example 106 to give the hydrochloride (180 mg) of the title compound as a white powder (yield: 1.4%).
m.p. (hydrochloride): 209 - 211°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ (ppm) 1.83-2.09(4H, m), 2.83-2.96(2H, m), 2.98-3.10(4H, m), 3.20-3.29(2H, m), 3.31-3.45(2H, m), 3.60-3.80(3H, m), 3.69(3H, s), 4.24-4.34(1H, m), 6.58-6.70(2H, m), 6.75-6.80(1H, m), 7.11-7.20(2H, m), 7.29-7.40(2H, m).

FAB-Mass: 355(MH+).

Example 100-1: Synthesis of 1-(4-fluorophenethyl)-4-(3-bromophenyl)aminopiperidine



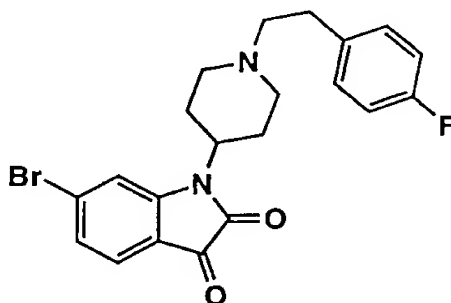
A solution of o-bromoaniline (17.2 g) and 4-fluorophenethylpiperidone (22 g) in toluene (200 ml) was heated under reflux overnight by using a Dean-Starke reflux condenser. After concentrating under reduced pressure, the residue was diluted with 1,2-dichloroethane (200 ml) and sodium borohydride (7.6 g) and acetic acid (8.0 g) were added thereto followed by stirring the resultant mixture at 0°C for 4 hr. Next, a saturated aqueous solution of sodium bicarbonate and ethyl acetate were added to the reaction solution and the layers were separated. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The residue was purified by silica gel column chromatography (methylene chloride/ethanol system) to give the title compound (10 g) as a brown oil (yield: 27%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.42-1.60(2H, m), 2.02-2.10(2H, m), 2.18-2.25(2H, m), 2.55-2.63(2H, m), 2.78-2.84(2H, m), 2.90-3.00(2H, m),

3.23-3.32(1H, m), 3.60(1H, d, J=8Hz), 6.50(1H, d, J=8Hz), 6.72(1H, s), 6.79(1H, d, J=8Hz), 6.94-7.02(3H, m), 7.12-7.20(2H, m).

Example 100-2: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-2,3-dioxo-6-bromoindoline



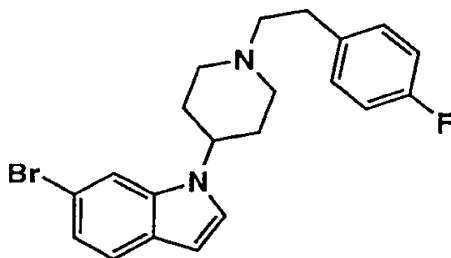
A solution of 1-(4-fluorophenethyl)-4-(3-bromophenyl)aminopiperidine (10 g) and oxalyl chloride (6.7 g) in ether (200 ml) was heated under reflux for 2 hr. After concentrating under reduced pressure, the residue was diluted with methylene chloride (200 ml) and the resultant solution was added dropwise at 0°C into a solution of anhydrous aluminum chloride (24.7 g) in methylene chloride (60 ml). After stirring for 1 hr, the reaction solution was carefully added to a saturated aqueous solution of sodium bicarbonate. The resulting crystalline precipitates were filtered off and washed with methylene chloride and the filtrate was partitioned between two liquid layers. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The resulting residue was purified by silica gel column

chromatography (hexane/ethyl acetate system) to give the title compound (7.4 g) as a yellow powder (yield: 65%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.75-1.83(2H, m), 2.15-2.25(2H, m), 2.35-2.50(2H, m), 2.60-2.69(2H, m), 2.78-2.87(2H, m), 3.11-3.20(2H, m), 4.12-4.28(1H, m), 6.95-7.03(2H, m), 7.15-7.20(2H, m), 7.28(1H, d, J=8Hz), 7.36(1H, s), 7.49(1H, d, J=8Hz).

Example 100-3: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-bromoindole



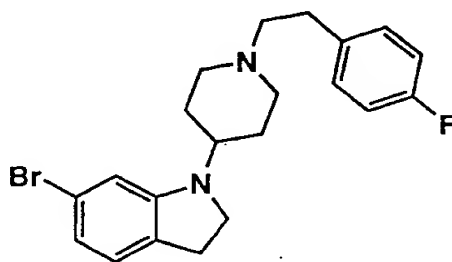
Under ice cooling, a 1 M solution (69 ml) of a borane/tetrahydrofuran complex in tetrahydrofuran was added dropwise into a solution of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-2,3-dioxo-6-bromoindoline (7.4 g) in tetrahydrofuran (150 ml) followed by stirring at room temperature overnight and heating under reflux for 3 hr. Into the reaction solution was carefully added dropwise a saturated aqueous solution of sodium bicarbonate. Then ethyl acetate was added to the resultant mixture and the organic layer was separated. The organic layer was washed with brine, dried over

anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was then diluted with pyridine (50 ml) and stirred at room temperature for 4 hr. Next, a saturated aqueous solution of sodium bicarbonate and ethyl acetate were added thereto and the layers were separated. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (3.9 g) as a yellow oil (yield: 57%).

$^1\text{H-NMR}$ (400 MHz, CDCl_3):

δ (ppm) 2.01-2.12(4H, m), 2.20-2.32(2H, m), 2.61-2.69(2H, m), 2.79-2.86(2H, m), 3.13-3.21(2H, m), 4.10-4.21(1H, m), 6.48(1H, d, $J=2\text{Hz}$), 6.95-7.02(2H, m), 7.12-7.23(2H, m), 7.45-7.55(3H, m), 7.91(1H, t, $J=6\text{Hz}$).

Example 100-4: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-bromoindoline



Under ice cooling, a 1 M solution (20 ml) of a borane/tetrahydrofuran complex in tetrahydrofuran was added dropwise into a solution of 1-[1-(4-fluorophenethyl)-

033486-05064
10200-62080
piperidin-4-yl]-6-bromoindole (3.9 g) in trifluoroacetic acid (50 ml) followed by stirring for 3 hr. After adding water thereto and concentrating under reduced pressure, the reaction mixture was basified by adding ethanol and a 5 N aqueous solution of sodium hydroxide and then stirred for 30 min. Next, a saturated aqueous solution of sodium bicarbonate and ethyl acetate were added thereto and the layers were separated. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The residue was then purified by silica gel column chromatography (toluene/acetone system) to give the title compound (2.0 g) as a white powder (yield: 51%).

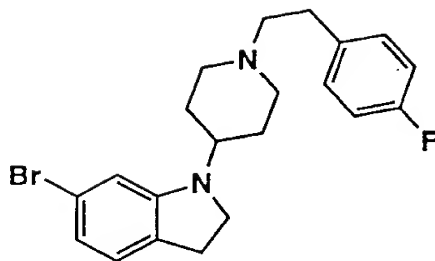
m.p.: 99 - 101°C.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.74-1.84(4H, m), 2.10-2.19(2H, m), 2.58-2.64(2H, m), 2.78-2.84(2H, m), 2.89(2H, t, J=8Hz), 3.10-3.17(2H, m), 3.28-3.38(1H, m), 3.43(2H, t, J=8Hz), 6.47(1H, d, J=2Hz), 6.69(1H, dd, J=2,8Hz), 6.87(1H, d, J=8Hz), 6.96-7.00(2H, m), 7.15-7.18(2H, m).

FAB-Mass: 404(MH+).

Example 101: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-bromoindoline



0334633, 033601
Triacetoxylated sodium borohydride (298 g) was added over 30 min to a mixture of 6-bromoindoline (175 g), 1-(4-fluorophenethyl)-4-piperidone (194 g), acetic acid (250 ml) and dichloroethane (2.5 l) followed by stirring 2 hr. Then the reaction solution was concentrated under reduced pressure, diluted with ethyl acetate (2 l), an 8 N aqueous solution of sodium hydroxide (1 l) and water (500 ml) and the layers were separated. The organic layer was washed successively with water (0.5 l) and brine (0.5 l), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was dissolved in hot ethyl acetate (500 ml) and then cooled with ice water. The resulting crystalline precipitates were collected by filtration to give the title compound (205 g) (yield: 58%).

These crude crystals were recrystallized from hexane-ethyl acetate mixtures to give the title compound as white prisms.

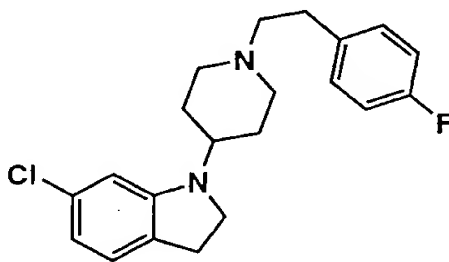
m.p.: 99 - 101°C.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.74-1.84(4H, m), 2.10-2.19(2H, m), 2.58-2.64(2H, m), 2.78-2.84(2H, m), 2.89(2H, t, J=8Hz), 3.10-3.17(2H, m), 3.28-3.38(1H, m), 3.43(2H, t, J=8Hz), 6.47(1H, d, J=2Hz), 6.69(1H, dd, J=2,8Hz), 6.87(1H, d, J=8Hz), 6.96-7.00(2H, m), 7.15-7.18(2H, m).

FAB-Mass: 404(MH+).

Example 102: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-chloroindoline



1-(4-Fluorophenethyl)-4-(3-chlorophenyl)-aminopiperidine (1.4 g) synthesized in accordance with the method of Referential Example 1 of JP-B 40-6347 was treated as in Example 101 to give the hydrochloride (380 mg) of the title compound as a white powder (yield: 25%).

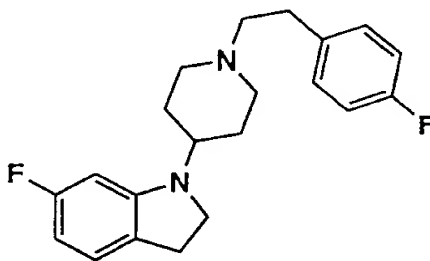
m.p. (hydrochloride): 236 - 240°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.79-1.90(2H, m), 1.99-2.12(2H, m), 2.87(2H, t, J=8Hz), 3.00-3.13(4H, m), 3.20-3.29(2H, m), 3.36(2H, t, J=8Hz), 3.55-3.63(2H, m), 3.70-3.80(1H, m), 6.52(1H, d, J=8Hz), 6.57(1H, s), 6.97(1H, d, J=8Hz), 7.13-7.20(2H, m), 7.29-7.35(2H, m).

FAB-Mass: 359(MH+).

Example 103: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-fluoroindoline



1-(Piperidin-4-yl)-6-fluoroindoline (200 mg) and 4-fluorophenethyl bromide (220 mg) were treated as in Example 2 to give the hydrochloride (220 mg) of the title compound as a white powder (yield: 65%).

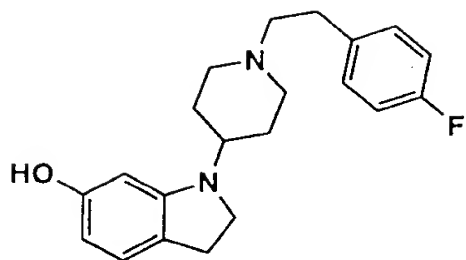
m.p. (hydrochloride): 214 - 216°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.81-1.90(2H, m), 1.95-2.08(2H, m), 2.85(2H, t, J=8Hz), 2.99-3.10(4H, m), 3.20-3.29(2H, m), 3.38(2H, t, J=8Hz), 3.67-3.75(3H, m), 6.26(1H, t, J=8Hz), 6.39(1H, d, J=8Hz), 6.95(1H, t, J=8Hz), 7.14-7.19(2H, m), 7.30-7.34(2H, m).

FAB-Mass: 343(MH+).

Example 104: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-hydroxyindoline



A solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methoxyindoline (1.6 g) in conc. hydrogen bromide (40 ml) was heated at 100°C for 2 hr. Next, it was basified with a conc. aqueous solution of sodium hydroxide and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (methylene chloride/ethanol system) followed by conversion into a hydrochloride in a conventional manner. Thus the hydrochloride (1.2 g) of the title compound was obtained as brown prisms (yield: 68%).

m.p. (hydrochloride): 232°C (decomp.).

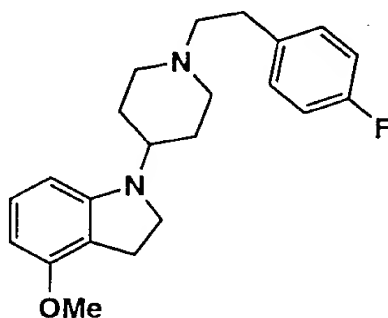
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.81-2.00(4H, m), 2.73(2H, t, J=8Hz), 2.97-3.12(4H, m), 3.21-3.33(4H, m), 3.59-3.69(3H, m), 5.93(1H, s), 5.97(1H, d, J=8Hz), 6.75(1H, d, J=8Hz), 7.12-7.21(2H, m), 7.30-7.38(2H, m), 8.89(1H, s).

FAB-Mass: 341(MH+).

Example 105: Synthesis of 1-[1-(4-

fluorophenethyl)piperidin-4-yl]-4-methoxyindoline



A mixture of 4-methoxyindoline (0.25 g), 1-(4-fluorophenethyl)-4-piperidone, platinum oxide (50 mg), acetic acid (1.0 ml) and ethanol (20 ml) was catalytically reduced under hydrogen atmosphere at ordinary temperature under atmospheric pressure. After stirring the reaction mixture overnight, the catalyst was filtered off and the filtrate was concentrated under reduced pressure. Then it was diluted with a saturated aqueous solution of sodium bicarbonate and ethyl acetate and the layers were separated. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system) followed by conversion into a hydrochloride in a conventional manner. Thus the hydrochloride (92 mg) of the title compound was obtained as a white powder (yield: 27%).

m.p. (hydrochloride): 195 - 198°C.

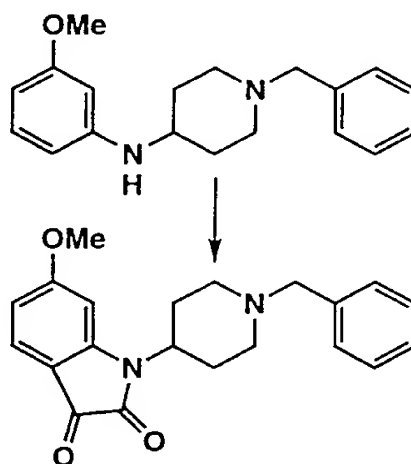
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.81-2.04(4H, m), 2.79(2H, t, J=8Hz), 3.00-3.13(4H,

m), 3.21-3.36(4H, m), 3.59-3.71(3H, m), 3.72(3H, s), 6.22(1H, d, J=8Hz), 6.27(1H, d, J=8Hz), 6.98(1H, t, J=8Hz), 7.15-7.20(2H, m), 7.31-7.35(2H, m).

FAB-Mass: 355(MH+).

Example 106-1: Synthesis of 1-(1-benzylpiperidin-4-yl)-6-methoxyindoline-2,3-dione



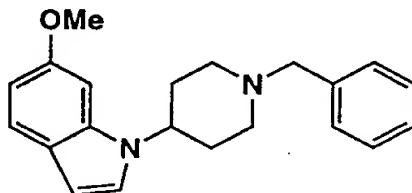
1-Benzyl-4-(3-methoxyphenyl)aminopiperidine (1.88 g) synthesized in accordance with the method of Referential Example 1 of JP-B 40-6347 was dissolved in ether (38 ml). Into the resultant solution was added dropwise oxalyl chloride (1.62 g) over 30 min at room temperature followed by heating under reflux for 3.5 hr. After cooling to room temperature, the reaction solution was concentrated under reduced pressure. Into a suspension of aluminum chloride (5.9 g) in methylene chloride (20 ml) was added dropwise a solution of the resulting residue in methylene chloride (100 ml) at 0°C over 30 min. After

the completion of the addition, the resultant mixture was stirred at room temperature for additional 1.5 hr. After the completion of the reaction, the reaction solution was poured into ice and neutralized by adding an aqueous solution of sodium bicarbonate thereto. The resulting precipitate was filtered off and the filtrate was extracted with methylene chloride. After removing the solvent, the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give 1-(1-benzylpiperidin-4-yl)-6-methoxyindoline-2,3-dione (1.63 g) (yield: 73%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.69-1.76(2H, m), 2.12(2H, br-t), 2.42(2H, dq, J=12.0, 4.0Hz), 3.03(2H, br-d), 3.55(2H, s), 3.93(3H, s), 4.08-4.18(1H, m), 6.54(1H, dd, J=8.4, 1.6Hz), 6.66(1H, d, J=1.6Hz), 7.24-7.36(5H, m), 7.59(1H, d, J=8.4Hz).

Example 106-2: Synthesis of 1-(1-benzylpiperidin-4-yl)-6-methoxyindole



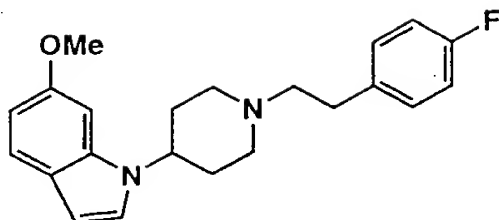
A 2 M solution (0.47 ml) of a diborane/dimethyl sulfide complex in tetrahydrofuran was added to a solution of 1-(1-benzylpiperidin-4-yl)-6-methoxyindoline-2,3-dione (110 mg)

in tetrahydrofuran (2 ml) followed by stirring for 1 hr and then heating under reflux for 4.5 hr. After the completion of the reaction, an aqueous solution of sodium bicarbonate was added to the reaction solution, which was then extracted with ethyl acetate. The ethyl acetate layer was dried over magnesium sulfate and the solvent was removed. The residue was dissolved in pyridine and stirred for 4.5 hr. After evaporating off pyridine, ethyl acetate and an aqueous solution of sodium bicarbonate were added thereto. The ethyl acetate layer was separated and dried over magnesium sulfate. After distilling off the solvent, the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give 1-(1-benzylpiperidin-4-yl)-6-methoxyindole (28 mg) (yield: 28%).

$^1\text{H-NMR}$ (400 MHz, CDCl_3):

δ (ppm) 2.02-2.12(4H, m), 2.17-2.27(2H, m), 3.07(2H, br-d), 3.60(2H, s), 3.87(3H, s), 4.09-4.18(1H, m), 6.44(1H, d, $J=3.2\text{Hz}$), 6.78(1H, dd, $J=8.8, 2.0\text{Hz}$), 6.82(1H, br-d), 7.13(1H, d, $J=3.2\text{Hz}$), 7.25-7.37(5H, m), 7.49(1H, d, $J=8.8\text{Hz}$).

Example 106-3: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methoxyindole



1-Chloroethyl chloroformate (32 mg) was added to a solution of 1-(1-benzylpiperidin-4-yl)-6-methoxyindole (24 mg) in toluene (2 ml) followed by heating under reflux for 3 hr. The reaction solution was concentrated under reduced pressure and the resulting residue was dissolved in methanol followed by heating under reflux for 9 hr. After the completion of the reaction, methanol was evaporated and the residue was dissolved in dimethylformamide (1 ml). Next, 2-(4-fluorophenyl)ethyl bromide (19 mg) was added thereto and the resultant mixture was stirred at 60°C for 11 hr. After the completion of the reaction, brine was added to the mixture. Then it was extracted with ethyl acetate and dried over magnesium sulfate. After removing the solvent, the resulting residue was purified by silica gel column chromatography (toluene/acetone system) to give the title compound (7 mg) (yield: 27%).

m.p.: 230°C (decomp.).

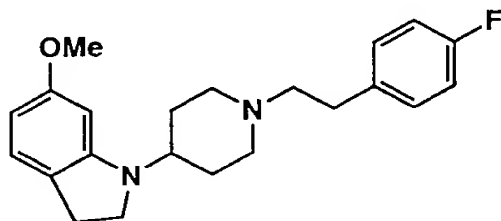
¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 2.06-2.14(4H, m), 2.25-2.33(2H, m), 2.67(2H, dd, J=9.2, 10.8Hz), 2.83(2H, dd, J=10.8, 9.2Hz), 3.20(2H, br-d,

J=11.6Hz), 3.88(3H, s), 4.12-4.21(1H, m), 6.45(1H, d, J=3.2Hz), 6.79(1H, dd, J=8.4, 2.0Hz), 6.83(1H, d, J=2.0Hz), 6.99(2H, t, J=12.4Hz), 7.14(1H, d, J=3.2Hz), 7.18(2H, dd, J=8.4, 5.6Hz), 7.50(1H, d, J=8.4Hz).

MS; [M+H]⁺: m/z=353.

Example 106-4: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methoxyindoline



A 1 M solution (0.18 ml) of a borane/tetrahydrofuran complex was added dropwise at 0°C into a solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methoxyindole (24 mg) in trifluoroacetic acid (1 ml) over 2 min followed by stirring at 0°C for 30 min. After the completion of the reaction, water (0.1 ml) was added thereto and the resulting reaction solution was concentrated under reduced pressure. The resulting residue was dissolved in a 2 N aqueous solution of sodium hydroxide and stirred at room temperature for 10 min. The mixture was extracted with methylene chloride. The organic layer was separated and dried over magnesium sulfate. After concentrating the solvent under reduced pressure, the resulting residue was purified by preparative TLC to give 1-[1-(4-

fluorophenethyl)piperidin-4-yl]]-6-methoxyindoline (10 mg)
(yield: 35%).

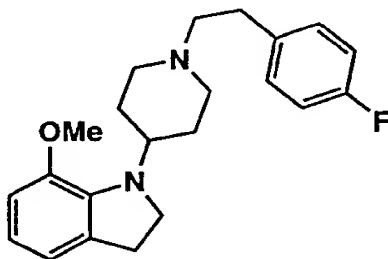
m.p.: 242°C (decomp.).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.75-1.90 (4H, m), 2.10-2.22 (2H, m), 2.58-2.70 (2H, m), 2.80 (2H, dd, J=11.6, 7.2Hz), 2.88 (2H, t, J=8.8Hz), 3.14 (2H, br-d, J=10.8Hz), 3.31-3.82 (1H, m), 3.41 (2H, t, J=8.4Hz), 3.77 (3H, s), 6.00 (1H, d, J=2.0Hz), 6.13 (1H, dd, J=8.0, 2.0Hz), 6.93 (1H, 2H, t, J=8.8Hz), 6.97 (2H, t, J=8.8Hz), 7.16 (2H, dd, J=8.4, 5.6Hz).

MS; [M+H]⁺: m/z=355.

Example 107: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-7-methoxyindoline



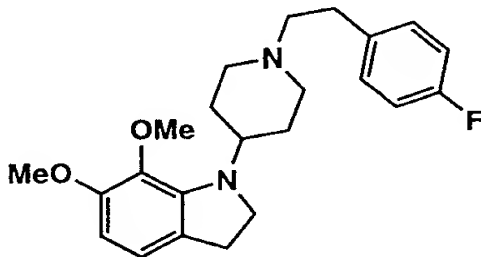
1-(4-Fluorophenethyl)-4-(2-methoxyphenyl)-aminopiperidine (3.9 g) synthesized in accordance with the method of Referential Example 1 of JP-B 40-6347 was treated as in Example 106 to give the hydrochloride (530 mg) of the title compound as a white powder (yield: 11%).
m.p. (hydrochloride): 204 - 206°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.72-1.80 (2H, m), 1.90-2.40 (2H, m), 2.86 (2H, t, J=8Hz), 2.95-3.08 (4H, m), 3.21-3.34 (4H, m), 3.55-3.63 (2H, m), 3.73 (3H, s), 4.24-4.34 (1H, m), 6.60-6.64 (1H, m), 6.69-6.74 (2H, m), 7.14-7.19 (2H, m), 7.28-7.32 (2H, m).

FAB-Mass: 355 (MH⁺).

Example 108: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6,7-dimethoxyindoline



1-(4-Fluorophenethyl)-4-(2,3-dimethoxyphenyl)amino-piperidine (8.1 g) synthesized in accordance with the method of Referential Example 1 of JP-B 40-6347 was treated as in Example 106 to give the oxalate (34 mg) of the title compound as a white powder (yield: 1.7%).

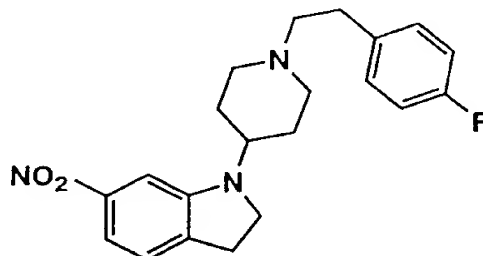
m.p. (oxalate): 179 - 181°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.72-1.86 (4H, m), 2.79 (2H, t, J=8Hz), 2.86-2.97 (2H, m), 3.04-3.18 (2H, m), 3.29 (2H, t, J=8Hz), 3.40-3.58 (4H, m), 3.64 (3H, s), 3.69 (3H, s), 4.05-4.17 (1H, m), 6.25 (1H, d, J=8Hz), 6.69 (1H, d, J=8Hz), 7.13-7.18 (2H, m), 7.28-7.32 (2H, m).

FAB-Mass: 385 (MH+).

Example 109: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-nitroindoline

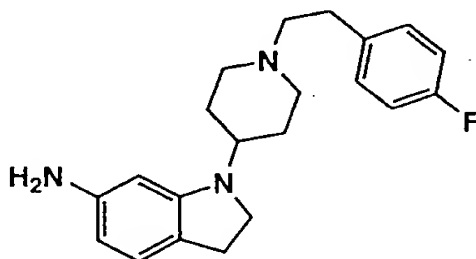


1-(Piperidin-4-yl)-6-nitroindoline (3.5 g) and 4-fluorophenethyl bromide (4.1 g) were treated as in Example 2 to give the title compound (5.1 g) as a pale yellow powder (yield: 81%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.71-2.89 (4H, m), 2.09-2.20 (2H, m), 2.55-2.66 (2H, m), 2.76-2.83 (2H, m), 3.03 (2H, t, J=8Hz), 3.10-3.19 (2H, m), 3.39-3.49 (1H, m), 3.56 (2H, t, J=8Hz), 6.95-7.00 (2H, m), 7.09 (1H, d, J=8Hz), 7.10 (1H, s), 7.12-7.21 (2H, m), 7.50 (1H, d, J=8Hz).

Example 110: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminoindoline



A mixture of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-

6-nitroindoline (5.1 g), powdery iron (5.0 g), ammonium chloride (10 g), water (20 ml) and ethanol (100 ml) was stirred at 60°C for 4 hr. Next, the reaction solution was filtered and the filtrate was concentrated under reduced pressure. Then a 5 N aqueous solution of sodium hydroxide and ethyl acetate were added thereto and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Then the resulting residue was purified by silica gel column chromatography (methylene chloride/ethanol system) to give the title compound (3.4 g) as a brown powder (yield: 73%).

m.p.: 104 - 106°C.

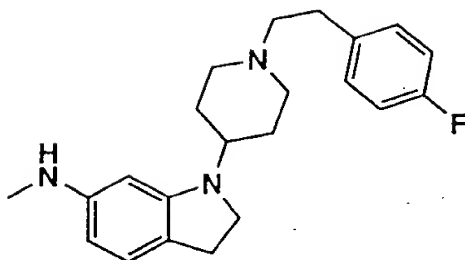
¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.69-1.88(4H, m), 2.05-2.13(2H, m), 2.53-2.60(2H, m), 2.71-2.81(2H, m), 2.83(2H, t, J=8Hz), 3.09-3.13(2H, m), 3.29-3.35(1H, m), 3.36(2H, t, J=8Hz), 3.50(2H, br-s), 5.82(1H, s), 5.98(1H, d, J=8Hz), 6.81(1H, d, J=8Hz), 6.91-7.00(2H, m), 7.12-7.20(2H, m).

FAB-Mass: 340(MH+).

Example 111: Synthesis of 1-[1-(4-

fluorophenethyl)piperidin-4-yl]-6-methylaminoindoline



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Ethyl chlorocarbonate (100 mg) was added dropwise at room temperature into a solution of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-aminoindoline (0.3 g) and triethylamine (100 mg) in methylene chloride (5 ml). Then the resultant mixture was stirred for 30 min and concentrated under reduced pressure. The resulting residue was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was added to a suspension of lithium aluminum hydride (67 mg) in tetrahydrofuran (5 ml) and heated under reflux for 1 hr. Under ice cooling, water (0.14 ml), a 5 N aqueous solution (0.42 ml) of sodium hydroxide and further water (0.14 ml) were carefully added dropwise into the reaction solution followed by vigorous stirring. The resulting precipitate was filtered off and the filtrate was concentrated under reduced pressure. Next, the obtained residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) followed by conversion into a hydrochloride in a conventional manner. Thus the

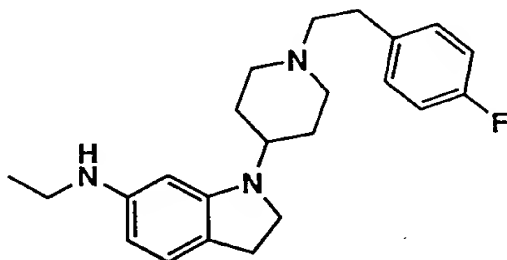
hydrochloride (220 mg) of the title compound was obtained as a brown hygroscopic amorphous solid (yield: 64%).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.81-1.90(2H, m), 1.99-2.13(2H, m), 2.82(3H, s), 2.90(2H, t, J=8Hz), 3.00-3.12(4H, m), 3.20-3.33(2H, m), 3.41(2H, t, J=8Hz), 3.59-3.69(2H, m), 3.80-3.90(1H, m), 6.56-6.62(2H, m), 7.09(1H, d, J=8Hz), 7.12-7.20(2H, m), 7.29-7.35(2H, m).

FAB-Mass: 354(MH⁺).

Example 112: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-ethylaminoindoline



A mixture of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminoindoline (0.3 g), pyridine (5 ml) and acetic anhydride (3 ml) was stirred at room temperature for 30 min. After concentrating the resultant mixture under reduced pressure, water and ethyl acetate were added thereto and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was added to a suspension of lithium aluminum hydride (127 mg) in tetrahydrofuran (5 ml) and heated

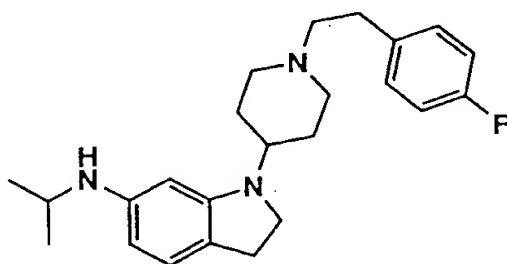
under reflux for 1 hr. Under ice cooling, water (0.14 ml), a 5 N aqueous solution (0.42 ml) of sodium hydroxide and further water (0.14 ml) were carefully added dropwise into the reaction solution followed by vigorous stirring. The resulting precipitate was filtered off and the filtrate was concentrated under reduced pressure. Next, the resulting residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) followed by conversion into a hydrochloride in a conventional manner. Thus the hydrochloride (210 mg) of the title compound was obtained as a pale brown hygroscopic amorphous solid (yield: 59%).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.20 (3H, t, J=7Hz), 1.82-1.91 (2H, m), 2.01-2.10 (2H, m), 2.89 (2H, t, J=8Hz), 3.00-3.09 (4H, m), 3.21-3.32 (4H, m), 3.39 (2H, t, J=8Hz), 3.60-3.72 (3H, m), 6.55-6.62 (2H, m), 7.09 (1H, d, J=8Hz), 7.10-7.21 (2H, m), 7.28-7.33 (2H, m).

FAB-Mass: 368 (MH⁺).

Example 113: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-isopropylaminoindoline



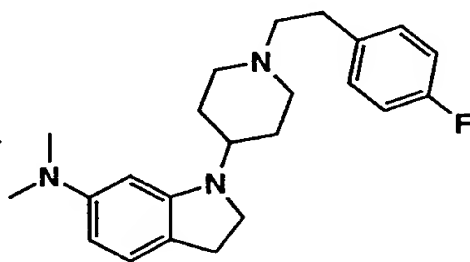
1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-aminoindoline (0.3 g), acetone (0.075 g), acetic acid (0.23 g) and triacetoxylated sodium borohydride (0.36 g) were treated as in Example 101 to give the hydrochloride (240 mg) of the title compound as a pale brown, hygroscopic and amorphous solid (yield: 65%).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.23 (6H, d, J=7Hz), 1.80-1.91 (2H, m), 2.02-2.20 (2H, m), 2.91 (2H, t, J=8Hz), 3.00-3.13 (4H, m), 3.20-3.29 (2H, m), 3.40 (2H, t, J=8Hz), 3.60-3.71 (4H, m), 6.61-6.69 (2H, m), 7.09 (1H, d, J=8Hz), 7.11-7.20 (2H, m), 7.31-7.39 (2H, m).

FAB-Mass: 382 (MH⁺).

Example 114: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-dimethylaminoindoline



6-Dimethylaminoindoline (0.6 g), 1-(4-fluorophenethyl-4-piperidone (0.98 g), acetic acid (1.1 g) and triacetoxylated sodium borohydride (1.2 g) were treated as in Example 101 to give the hydrochloride (0.77 g) of the title compound as a white powder (yield: 52%).

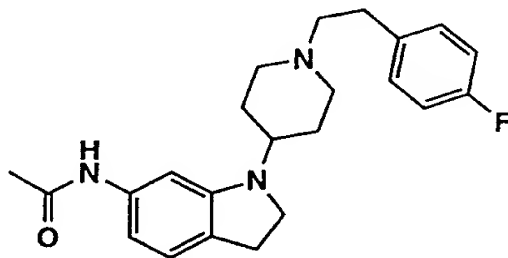
m.p. (hydrochloride): 205 - 208°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.81-2.03 (4H, m), 2.71 (2H, t, J=8Hz), 2.80 (6H, s), 2.99-3.13 (4H, m), 3.20-3.31 (4H, m), 3.53-3.67 (2H, m), 3.70-3.80 (1H, m), 5.89-5.99 (2H, m), 6.80 (1H, d, J=8Hz), 7.11-7.19 (2H, m), 7.29-7.36 (2H, m).

FAB-Mass: 367 (MH⁺).

Example 115: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-acetamidoindoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-aminoindoline (1.0 g) and acetic anhydride (1 ml) were treated as in Example 133 to give the title compound (450 mg) as a pale yellow powder (yield: 41%).

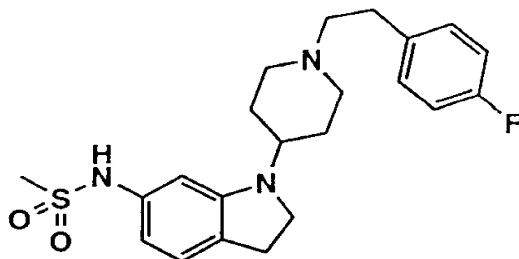
m.p.: 148 - 150°C.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.80-1.91 (4H, m), 2.15 (3H, s), 2.20-2.35 (2H, m), 2.62-2.75 (2H, m), 2.81-2.97 (2H, m), 2.90 (2H, t, J=8Hz), 3.13-3.29 (2H, m), 3.39-3.48 (1H, m), 3.42 (2H, t, J=8Hz), 6.44 (1H, d, J=8Hz), 6.93-7.01 (4H, m), 7.16-7.20 (3H, m).

FAB-Mass: 382 (MH⁺) .

Example 116: Synthesis of 1-[1-(4-fluorophenethyl)-
piperidin-4-yl]-6-methanesulfonylaminindoline



Methanesulfonyl chloride (0.4 g) was added dropwise at 0°C into a mixture of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminoindoline (0.3 g), 4-dimethylaminopyridine (0.1 g) and pyridine (10 ml) followed by stirring for 2 hr. Then water and ethyl acetate were added to the reaction solution and the layers were separated. The organic layer was washed with water and brine and dried over anhydrous magnesium sulfate. The residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) followed by conversion into a hydrochloride in a conventional manner. Thus the hydrochloride (160 mg) of the title compound was obtained as a pale yellow hygroscopic amorphous solid (yield: 40%).

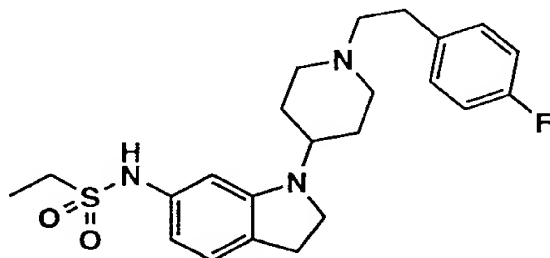
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.80-2.03 (4H, m), 2.85 (2H, t, J=8Hz), 2.89 (3H, s), 2.99-3.17 (4H, m), 3.20-3.43 (5H, m), 3.58-3.69 (2H, m), 6.37-6.40 (2H, m), 6.94 (1H, d, J=8Hz), 7.15-7.20 (2H, m), 7.30-7.34 (2H,

m), 9.33 (1H, s).

FAB-Mass: 418 (MH+).

Example 117: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-ethanesulfonylaminoindoline



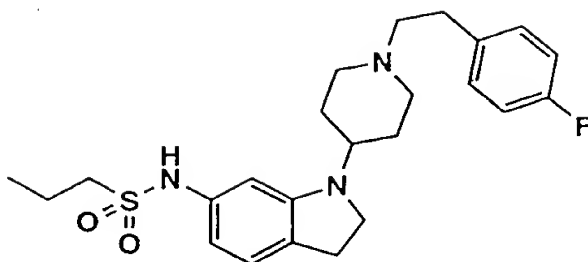
1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-aminoindoline (0.4 g) and ethanesulfonyl chloride (0.61 g) were treated as in Example 116 to give the hydrochloride (160 mg) of the title compound as a brown hygroscopic amorphous solid (yield: 29%).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.16 (3H, t, J=7Hz), 1.81-1.89 (2H, m), 1.94-2.05 (2H, m), 2.82 (2H, t, J=8Hz), 2.98 (2H, q, J=7Hz), 2.99-3.16 (4H, m), 3.20-3.29 (2H, m), 3.31 (2H, t, J=8Hz), 3.35-3.44 (1H, m), 3.55-3.68 (2H, m), 6.37-6.39 (2H, m), 6.93 (1H, d, J=8Hz), 7.13-7.19 (2H, m), 7.29-7.33 (2H, m), 9.42 (1H, s).

FAB-Mass: 432 (MH+).

Example 118: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-propanesulfonylaminoindoline



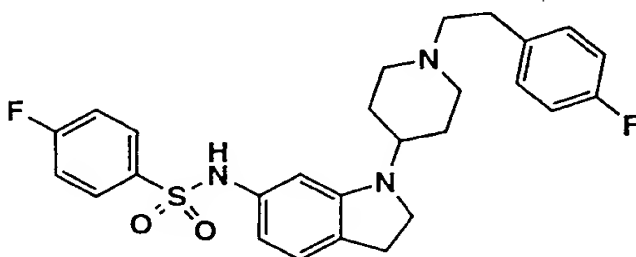
1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-aminoindoline (0.4 g) and propanesulfonyl chloride (0.67 g) were treated as in Example 116 to give the hydrochloride (210 mg) of the title compound as a white powder (yield: 37%).
m.p. (hydrochloride): 166 - 169°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 0.91(3H, t, J=7Hz), 1.65(2H, sextet, J=7Hz), 1.82-2.04(4H, m), 2.84(2H, t, J=8Hz), 2.94(2H, q, J=7Hz), 3.00-3.16(4H, m), 3.22-3.43(5H, m), 3.59-3.68(2H, m), 6.38-6.40(2H, m), 6.91(1H, d, J=8Hz), 7.11-7.20(2H, m), 7.30-7.38(2H, m), 9.41(1H, s).

FAB-Mass: 446(MH⁺).

Example 119: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(4-fluorobenzenesulfonylamino)indoline



6-(4-Fluorobenzenesulfonylamino)indoline (0.23 g), 1-(4-fluorophenethyl)-4-piperidone (0.33 g), acetic acid (0.36 g) and triacetoxylated sodium borohydride (0.42 g) were treated as in Example 101 to give the hydrochloride (0.29 g) of the title compound as a white powder (yield: 68%).

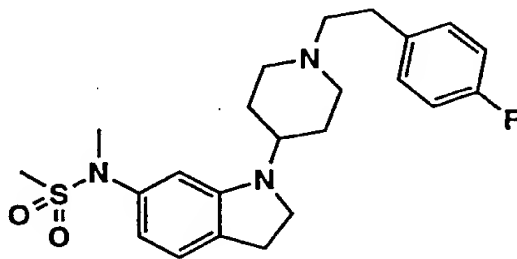
m.p. (hydrochloride): 140 - 143°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.69-1.73 (2H, m), 1.83-1.99 (2H, m), 2.75 (2H, t, J=8Hz), 3.01-3.19 (4H, m), 3.20-3.31 (4H, m), 3.51-3.63 (3H, m), 6.12 (1H, d, J=8Hz), 6.28 (1H, s), 6.81 (1H, d, J=8Hz), 7.13-7.21 (2H, m), 7.30-7.41 (4H, m), 7.74-7.79 (2H, m).

FAB-Mass: 498 (MH⁺).

Example 120: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(N-methylmethanesulfonylamino)indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-methylaminoindoline (150 mg) and methanesulfonyl chloride (54 mg) were treated as in Example 116 to give the hydrochloride (100 mg) of the title compound as white prisms (yield: 55%).

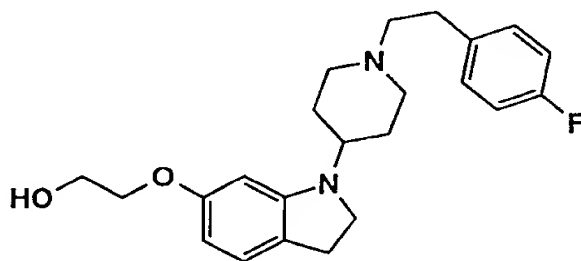
m.p. (hydrochloride): 136 - 139°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ (ppm) 1.82-1.89 (2H, m), 1.98-2.10 (2H, m), 2.83-2.90 (2H, m), 2.90 (3H, s), 3.01-3.14 (4H, m), 3.17 (3H, s), 3.20-3.28 (2H, m), 3.32-3.40 (2H, m), 3.58-3.76 (3H, m), 6.54-6.59 (2H, m), 7.01 (1H, d, J=8Hz), 7.14-7.19 (2H, m), 7.30-7.34 (2H, m).

FAB-Mass: 432 (MH⁺).

Example 121: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-hydroxyethoxyindoline



60% sodium hydride (0.11 g) was added to a solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-hydroxyindoline (0.8 g) in dimethylformamide (30 ml) and the resultant mixture was stirred at 50°C. After 10 min, (t-butyl)dimethylsiloxylethyl bromide (0.67 g) was added to the reaction solution followed by stirring for additional 2 hr. Then the mixture was concentrated under reduced pressure, diluted with a 2 N aqueous solution of sodium hydroxide and ethyl acetate and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethanol system). To the

residue were added a 1 M solution (2.4 ml) of tetrabutylammonium fluoride in tetrahydrofuran and tetrahydrofuran (20 ml) and the resultant mixture was stirred at room temperature for 3 hr. Next, the mixture was diluted with a 2 N aqueous solution of sodium hydroxide and ethyl acetate and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethanol system) followed by conversion into a hydrochloride in a conventional manner to give the hydrochloride (300 mg) of the title compound as a white powder (yield: 25%).

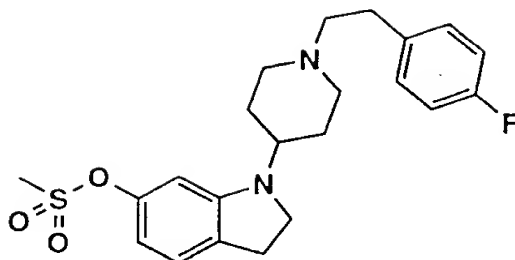
m.p. (hydrochloride): 235 - 238°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.84-1.99 (2H, m), 2.79 (2H, t, J=8Hz), 2.97-3.14 (4H, m), 3.22-3.34 (4H, m), 3.60-3.77 (5H, m), 3.88 (2H, t, J=5Hz), 4.79 (1H, br-s), 6.09 (1H, d, J=8Hz), 6.12 (1H, s), 6.88 (1H, d, J=8Hz), 7.12-7.20 (2H, m), 7.30-7.38 (2H, m).

FAB-Mass: 385 (MH+).

Example 122: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-methanesulfonyloxyindoline



A solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methoxyindoline (1.0 g) in conc. hydrogen bromide (20 ml) was heated at 100°C for 2 hr. Next, the mixture was basified with a conc. aqueous solution of sodium hydroxide and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in pyridine (10 ml) and methanesulfonyl chloride (0.46 g) was added dropwise thereinto under ice cooling. After stirring overnight, the resultant mixture was concentrated under reduced pressure, diluted with a 2 N aqueous solution of sodium hydroxide and ethyl acetate and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Then the residue was purified by NH-silica gel column chromatography (ethyl acetate/hexane system) followed by conversion into a hydrochloride in a conventional manner to give the hydrochloride (300 mg) of the title compound as a pale brown powder (yield: 15%).

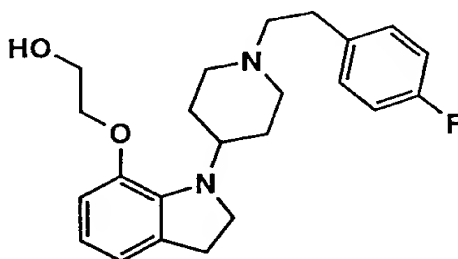
m.p. (hydrochloride): 220 - 223°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.83-1.92 (2H, m), 1.94-2.06 (2H, m), 2.90 (2H, t, J=8Hz), 3.00-3.14 (4H, m), 3.21-3.28 (2H, m), 3.30 (3H, s), 3.34-3.44 (2H, m), 3.59-3.66 (2H, m), 3.68-3.78 (1H, m), 6.46-6.48 (2H, m), 7.04 (1H, d, J=8Hz), 7.15-7.19 (2H, m), 7.30-7.34 (2H, m).

FAB-Mass: 419 (MH⁺).

Example 123: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-7-hydroxyethoxyindoline



A solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-7-methoxyindoline (0.3 g) in conc. hydrogen bromide (6 ml) was heated at 100°C for 2 hr. Then the solution was basified with a conc. aqueous solution of sodium hydroxide and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was dissolved in dimethylformamide (10 ml) and 60% sodium hydride (32 mg) was added thereto followed by stirring at 50°C. After 30 min,

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(t-butyl)dimethylsiloxyethyl bromide (0.19 g) was added to the reaction solution and the resultant mixture was stirred for additional 30 min. After concentrating under reduced pressure, it was diluted with a 2 N aqueous solution of sodium hydroxide and ethyl acetate and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol system). To the residue were added a 1 M solution (0.45 ml) of tetrabutylammonium fluoride in tetrahydrofuran and tetrahydrofuran (10 ml) and the resultant mixture was stirred at room temperature overnight. Then it was diluted with a 2 N aqueous solution of sodium hydroxide and ethyl acetate and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol system) followed by conversion into a hydrochloride in a conventional manner to give the hydrochloride (80 mg) of the title compound as a white, hygroscopic and amorphous solid (yield: 25%).

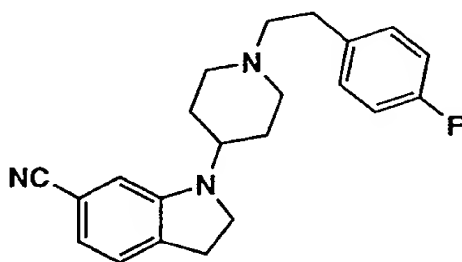
$^1\text{H-NMR}$ (400 MHz, DMSO-d_6):

δ (ppm) 1.79-1.86 (2H, m), 1.95-2.07 (2H, m), 2.91 (2H, t, $J=8\text{Hz}$), 2.95-3.07 (4H, m), 3.20-3.27 (2H, m), 3.30-3.41 (2H, m),

3.56-3.63 (2H, m), 3.74 (2H, t, J=5Hz), 3.96 (2H, t, J=5Hz),
4.38-4.47 (1H, m), 6.69-6.80 (3H, m), 7.11-7.21 (2H, m), 7.29-
7.35 (2H, m).

FAB-Mass: 385 (MH+).

Example 124: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-cyanoindoline



Trifluoromethanesulfonic anhydride (0.72 ml) was added dropwise at -78°C into a solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-hydroxyiminomethylindoline (1.5 g) and triethylamine (1.2 ml) in methylene chloride (1 l) and the resultant mixture was warmed to room temperature. Next, a saturated aqueous solution of sodium bicarbonate and chloroform were added thereto and the layers were separated. The organic layer was dried over anhydrous magnesium sulfate and the residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (1.0 g) as a white powder (yield: 67%).

A portion of these crystals were converted into a hydrochloride in a conventional manner to give the

hydrochloride of the title compound as white powdery crystals.

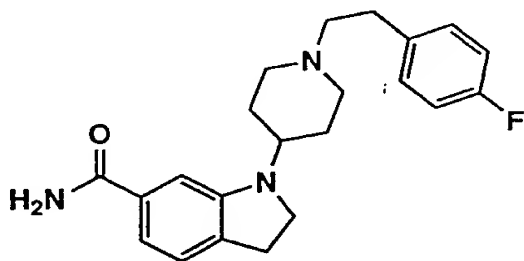
m.p. (hydrochloride): 230°C (decomp.).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.82-1.91(2H, m), 1.95-2.09(2H, m), 2.98(2H, t, J=8Hz), 3.00-3.13(4H, m), 3.21-3.30(2H, m), 3.41(2H, t, J=8Hz), 3.59-3.68(2H, m), 3.74-3.83(1H, m), 6.90(1H, s), 6.96(1H, d, J=8Hz), 7.11-7.20(3H, m), 7.30-7.39(2H, m), 10.51(1H, br-s).

FAB-Mass: 350(MH⁺).

Example 125: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-carbamoylindoline



A solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-cyanoindoline (1.0 g) in conc. sulfuric acid (1 l) was heated at 50°C for 2 hr. After diluting with ice water, the reaction solution was basified with a conc. aqueous solution of sodium hydroxide. Then ethyl acetate was added thereto and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound (0.81 g) as a white powder (yield: 77%).

A portion of these crystals were converted into a hydrochloride in a conventional manner to give the hydrochloride of the title compound as a white powder.

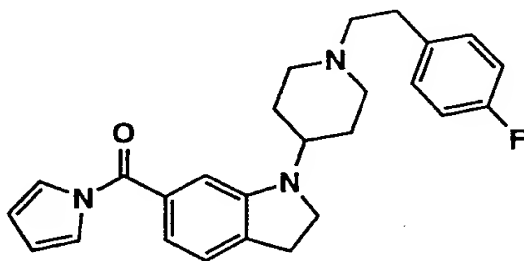
m.p. (hydrochloride): 160 - 162°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.87-1.95(2H, m), 1.99-2.13(2H, m), 2.94(2H, t, J=8Hz), 3.04-3.17(4H, m), 3.24-3.31(2H, m), 3.38(2H, t, J=8Hz), 3.60-3.68(2H, m), 3.73-3.83(1H, m), 7.01(1H, s), 7.07(1H, d, J=8Hz), 7.12(1H, d, J=8Hz), 7.16-7.21(3H, m), 7.32-7.36(2H, m), 7.79(1H, br-s).

FAB-Mass: 368(MH⁺).

Example 126: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(1-pyrrolylcarbonyl)indoline



A mixture of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-carbamoylindoline (0.3 g), 1,4-dichloro-1,4-dimethoxybutane (0.7 g), Amberlyst A-21 (0.5 g) and acetonitrile (10 ml) was heated at 60°C for 10 hr. After filtering, the reaction solution was basified with a saturated aqueous solution of sodium bicarbonate and then ethyl acetate

was added thereto and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) followed by conversion into an oxalate in a conventional manner to give the oxalate (0.13 g) of the title compound as a pale yellow powder (yield: 31%).

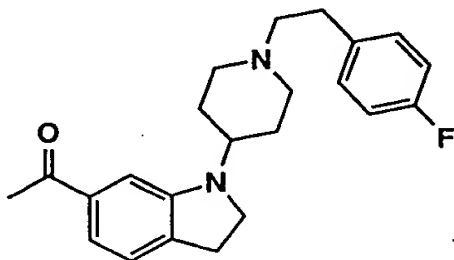
m.p. (oxalate): 169 - 171°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.83-1.94 (4H, m), 2.90-2.97 (4H, m), 3.02 (2H, t, J=8Hz), 3.08-3.19 (2H, m), 3.41-3.55 (4H, m), 3.72-3.83 (1H, m), 6.37 (2H, s), 6.80 (1H, s), 6.89 (1H, d, J=8Hz), 7.14-7.21 (3H, m), 7.28-7.34 (4H, m).

FAB-Mass: 418 (MH⁺).

Example 127: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-acetylindoline



A 2.5 M solution (1.5 ml) of n-butyllithium in hexane was added dropwise at -78°C into a solution (30 ml) of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-bromoindoline (1.0 g) in tetrahydrofuran over 5 min. After 10 min, dimethylacetamide

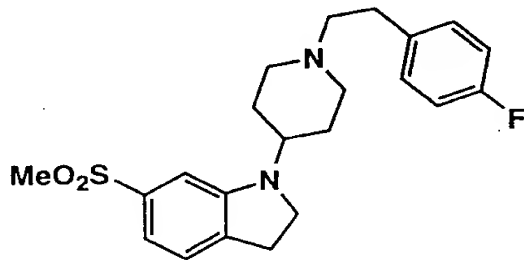
(0.34 ml) was added thereto and the resultant mixture was warmed to room temperature. Next, a saturated aqueous solution of ammonium chloride and ethyl acetate were added thereto to and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (250 mg) as a yellow powder (yield: 27%).
m.p.: 90 - 92°C.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.71-1.86 (4H, m), 2.12-2.22 (2H, m), 2.56 (3H, s), 2.57-2.64 (2H, m), 2.77-2.84 (2H, m), 2.99 (2H, t, J=8Hz), 3.07-3.16 (2H, m), 3.42-3.56 (1H, m), 3.46 (2H, t, J=8Hz), 6.94-6.99 (3H, m), 7.08 (1H, d, J=8Hz), 7.14-7.23 (3H, m).

FAB-Mass: 367 (MH⁺).

Example 128: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methanesulfonylindoline



A 2.5 M solution (0.6 ml) of n-butyllithium in hexane was added dropwise at -78°C into a solution of 1-[1-(4-

fluorophenethyl)piperidin-4-yl]-6-bromoindoline (470 mg) in tetrahydrofuran (20 ml) over 10 min. After 10 min, a saturated solution of sulfur dioxide in tetrahydrofuran (50 ml) was added thereto and the resultant mixture was warmed to room temperature. After concentrating the reaction solution under reduced pressure, dimethylformamide (10 ml) and methyl iodide (100 mg) were added to the residue and the resultant mixture was stirred at room temperature overnight. Then the reaction solution was concentrated under reduced pressure, a saturated aqueous solution of sodium bicarbonate and ethyl acetate were added thereto and the layers were separated. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) followed by conversion into a hydrochloride in a conventional manner to give the hydrochloride (20 mg) of the title compound as brown prisms (yield: 3.8%).

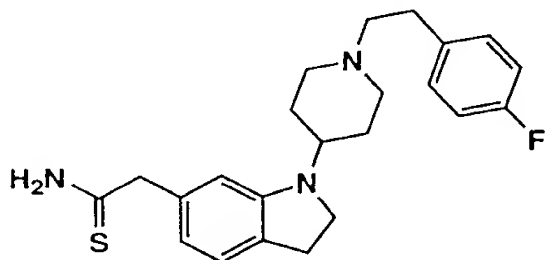
m.p. (hydrochloride): 228°C (decomp.).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.83-2.09(4H, m), 2.98-3.18(6H, m), 3.10(3H, s), 3.20-3.31(2H, m), 3.44(2H, t, J=8Hz), 3.59-3.68(2H, m), 3.80-3.93(1H, m), 6.91(1H, s), 7.06(1H, d, J=8Hz), 7.14-7.23(3H, m), 7.30-7.35(2H, m).

FAB-Mass: 403(MH+).

Example 129: Synthesis of 1-[1-(4-fluorophenethyl)-
piperidin-4-yl]-6-thiocarbamoylmethylindoline



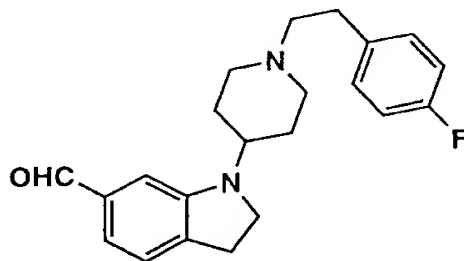
034623-050601
A mixture of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-carbamoylmethylindoline (720 mg), phosphorus pentasulfide (250 mg) and pyridine (20 ml) was heated under reflux for 1 hr. Then the mixture was diluted with a 5 N aqueous solution of sodium hydroxide and ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) followed by conversion into a hydrochloride in a conventional manner to give the hydrochloride (170 mg) of the title compound as a white hygroscopic amorphous solid (yield: 21%).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.86-1.94 (2H, m), 2.02-2.15 (2H, m), 2.86 (2H, t, J=8Hz), 3.03-3.16 (4H, m), 3.22-3.30 (2H, m), 3.33 (2H, t, J=8Hz), 3.60-3.74 (3H, m), 3.70 (2H, s), 6.57 (1H, d, J=8Hz), 6.61 (1H, s), 6.95 (1H, d, J=8Hz), 7.16-7.21 (2H, m), 7.32-7.36 (2H, m), 9.26 (1H, br-s), 9.42 (1H, br-s), 10.60 (1H, br-s).

FAB-Mass: 398 (MH⁺) .

Example 130: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-formylindoline



A 2.5 M solution (50 ml) of n-butyllithium in hexane was added dropwise at -78°C into a solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-bromoindoline (40 g) in tetrahydrofuran (1 l) over 10 min. After 10 min, dimethylformamide (11.6 ml) was added thereto and the resultant mixture was warmed to room temperature. Next, a saturated aqueous solution of ammonium chloride (200 ml) and ethyl acetate (500 ml) were added thereto and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the crude title compound (37.5 g). A portion of this crude product was purified by silica gel column chromatography (ethyl acetate/ethanol system) to give the title compound as a yellow powder.

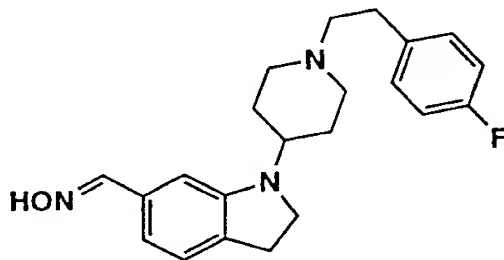
m.p.: 109 -111°C.

¹H-NMR (400 MHz, CDCl₃):

δ (ppm) 1.78-1.80(4H, m), 2.10-2.29(2H, m), 2.59-2.68(2H, m), 2.79-2.90(2H, m), 3.03(2H, t, J=8Hz), 3.10-3.19(2H, m), 3.42-3.53(1H, m), 3.50(2H, t, J=8Hz), 6.82(1H, s), 6.91-7.00(2H, m), 7.09(1H, d, J=8Hz), 7.13-7.19(3H, m), 9.85(1H, s).

FAB-Mass: 353(MH+).

Example 131: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-hydroxyiminomethylindoline



A suspension of crude 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-formylindoline (35 g), hydroxylammonium chloride (10.4 g) and anhydrous sodium acetate (12.3 g) in ethanol (400 ml) was stirred at room temperature for a day. Then the reaction solution was concentrated under reduced pressure, diluted with ethyl acetate (500 ml), an 8 N aqueous solution (30 ml) of sodium hydroxide and water (100 ml) and the layers were separated. The organic layer was washed with brine and dried over magnesium sulfate. After removing the solvent, the residue was dissolved in a hot toluene (100 ml)-isopropyl ether (100 ml) mixtures and allowed to cool at room temperature. The resulting crystals were collected by filtration and dried at

50°C to give the title compound (31 g) as a pale yellow powder (yield: 85%).

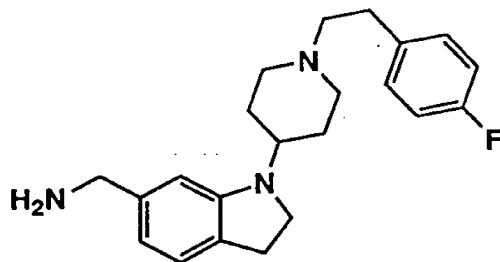
m.p.: 152 - 154°C.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.78-1.85(4H, m), 2.08-2.20(2H, m), 2.56-2.64(2H, m), 2.78-2.84(2H, m), 2.92(2H, t, J=8Hz), 3.10-3.19(2H, m), 3.40-3.50(1H, m), 3.46(2H, t, J=8Hz), 6.69(1H, s), 6.70(1H, d, J=8Hz), 6.92-7.00(2H, m), 7.03(1H, d, J=8Hz), 7.15-7.20(2H, m), 8.06(1H, s).

FAB-Mass: 368(MH+).

Example 132: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminomethylindoline



Under ice cooling and stirring, 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-hydroxyiminomethylindoline (31 g) was added in portions to a suspension of lithium aluminum hydride (8.0 g) in tetrahydrofuran (500 ml) and then the resultant mixture was heated under reflux for 3 hr. Under cooling with ice water, water (8 ml), a 5 N aqueous solution (24 ml) of sodium hydroxide and further water (8 ml) were

carefully added dropwise to the reaction solution followed by vigorous stirring. The resulting precipitate was filtered off and the filtrate was concentrated under reduced pressure to give the crude title compound (about 30 g). A portion of this crude product was purified by NH-silica gel column chromatography (ethyl acetate) and recrystallized from ethyl acetate-isopropyl ether mixtures to give the title compound as a pale yellow powder.

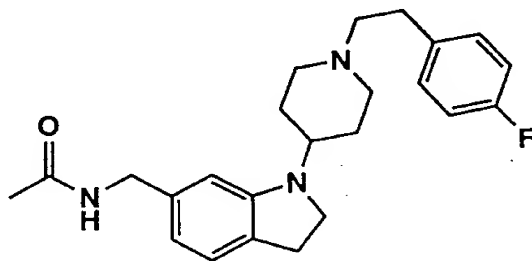
m.p.: 83 - 85°C.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.52-2.02 (6H, m), 2.10-2.20 (2H, m), 2.56-2.63 (2H, m), 2.78-2.83 (2H, m), 2.91 (2H, t, J=8Hz), 3.10-3.18 (2H, m), 3.37-3.50 (1H, m), 3.41 (2H, t, J=8Hz), 3.69 (2H, s), 6.39 (1H, s), 6.51 (1H, d, J=8Hz), 6.93-7.01 (3H, m), 7.12-7.20 (2H, m).

FAB-Mass: 354 (MH⁺).

Example 133: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindoline



Under ice cooling, acetyl chloride (6.6 ml) was added dropwise into a solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminomethylindoline (30 g)

obtained above and triethylamine (9.4 g) in acetonitrile (500 ml) and the resultant mixture was stirred at room temperature for 1 hr. After adding a 5 N aqueous solution (40 ml) of sodium hydroxide and water (500 ml) to the reaction solution, the resulting crystalline precipitates were collected by filtration, washed successively with water and ethyl acetate and then dried at 50°C overnight to give the crude title compound (22.8 g). This crude product was recrystallized successively from ethyl acetate and ethanol to give the title compound (17.9 g) as white needles (yield: 54%).

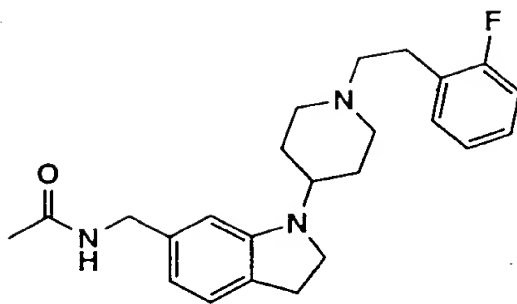
m.p.: 160 - 162°C.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.78-1.86(4H, m), 2.01(3H, s), 2.12-2.28(2H, m), 2.58-2.72(2H, m), 2.76-2.89(2H, m), 2.93(2H, t, J=8Hz), 3.08-3.26(2H, m), 3.35-3.46(1H, m), 3.42(2H, t, J=8Hz), 4.33(2H, d, J=6Hz), 5.69(1H, br-s), 6.34(1H, s), 6.51(1H, d, J=8Hz), 6.95-7.02(3H, m), 7.14-7.20(2H, m).

FAB-Mass: 396(MH+).

Example 134: Synthesis of 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindoline



1-(Piperidin-4-yl)-6-acetamidomethylindoline (250 mg) and 2-fluorophenethyl bromide (220 mg) were treated as in Example 2 to give the title compound (190 mg) as a white-powder (yield: 52%).

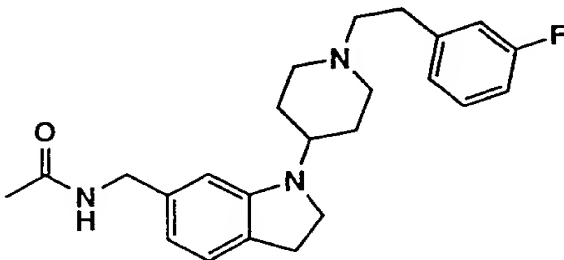
m.p.: 160 - 161°C.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.51-1.68 (2H, m), 1.81-1.92 (2H, m), 2.00 (3H, s), 2.20-2.40 (2H, m), 2.70-2.89 (4H, m), 2.91 (2H, t, J=8Hz), 3.01-3.10 (2H, m), 3.40-3.48 (3H, m), 4.32 (2H, d, J=6Hz), 6.39 (1H, s), 6.51 (1H, d, J=8Hz), 6.98-7.10 (3H, m), 7.18-7.30 (2H, m).

FAB-Mass: 396 (MH⁺).

Example 135: Synthesis of 1-[1-(3-fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindoline



1-(Piperidin-4-yl)-6-acetamidomethylindoline (250 mg)

and 3-fluorophenethyl bromide (220 mg) were treated as in Example 2 to give the title compound (210 mg) as white needles (yield: 58%).

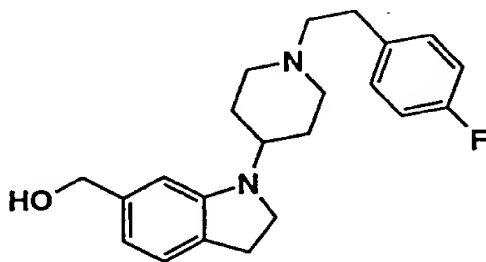
m.p.: 161 - 162°C.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.51-1.68(2H, m), 1.80-1.89(2H, m), 2.00(3H, s), 2.11-2.37(4H, m), 2.65-2.75(2H, m), 2.91(2H, t, J=8Hz), 3.12-3.29(2H, m), 3.40-3.48(3H, m), 4.32(2H, d, J=6Hz), 6.38(1H, s), 6.51(1H, d, J=8Hz), 6.98-6.98(2H, m), 7.00-7.05(2H, m), 7.21-7.30(1H, m).

FAB-Mass: 396(MH+).

Example 136: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-hydroxymethylindoline



A 2.5 M solution (100 ml) of n-butyllithium in hexane was added dropwise at -78°C into a solution (2 l) of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-bromoindoline (80 g) in tetrahydrofuran over 15 min. After 10 min, dimethylformamide (23.2 ml) was added thereto and the resultant mixture was warmed to room temperature. Next, a saturated aqueous solution of

ammonium chloride (400 ml) and ethyl acetate (1 l) were added thereto and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. To the resulting residue were added ethanol (240 ml) and sodium borohydride (7.6 g) and the resultant mixture was stirred at room temperature for 1 hr. After adding ice water (480 ml) to the reaction solution, the resulting crystals were collected by filtration, washed with water and air-dried at 50°C over day and night to give the title compound (about 71 g) as a yellow powder. A portion of this crude product was purified by silica gel column chromatography (ethyl acetate/methanol system) followed by conversion into a hydrochloride in a conventional manner to give the hydrochloride of the title compound as a pale purple powder. m.p. (hydrochloride): 190°C (decomp.).

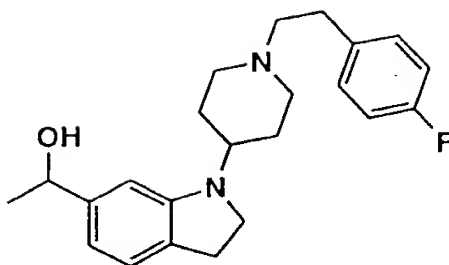
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.81-1.90 (2H, m), 1.99-2.11 (2H, m), 2.81-2.90 (2H, m), 3.02-3.13 (4H, m), 3.20-3.29 (2H, m), 3.31 (2H, t, J=8Hz), 3.68-3.63 (2H, m), 3.70-3.80 (1H, m), 4.38 (2H, s), 6.30-6.37 (2H, m), 6.96 (1H, d, J=8Hz), 7.12-7.20 (2H, m), 7.30-7.36 (2H, m), 10.60 (1H, br-s).

FAB-Mass: 355 (MH⁺).

Example 137: Synthesis of 1-[1-(4-

fluorophenethyl)piperidin-4-yl]-6-(1-hydroxyethyl)indoline



Sodium borohydride (0.03 g) was added to a solution (5 ml) of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-acetylin-3H-indole (0.17 g) in ethanol and the resultant mixture was stirred at room temperature overnight. Then ethyl acetate and water were added to the reaction solution and the layers were separated. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. Then the residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (150 mg) as a colorless oil (yield: 89%).

To a solution of this oily substance in acetone, oxalic acid (37 mg) was added to give the oxalate (140 mg) of the title compound as a gray powder.

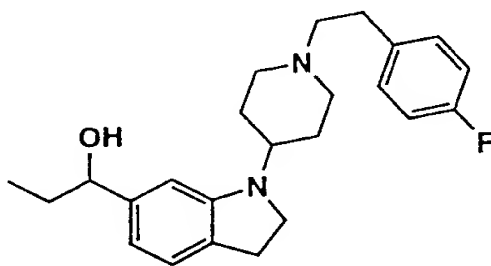
m.p. (oxalate): 113 - 116°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.28(3H, d, J=6Hz), 1.84-2.05(4H, m), 2.84(2H, t, J=8Hz), 3.00-3.35(8H, m), 3.55-3.68(2H, m), 3.70-3.80(1H, m), 4.61(1H, q, J=6Hz), 6.52-6.54(2H, m), 6.94(1H, d, J=8Hz), 7.16-7.21(2H, m), 7.32-7.36(2H, m).

FAB-Mass: 369 (MH⁺) .

Example 138: Synthesis of 1-[1-(4-fluorophenethyl)-
piperidin-4-yl]-6-(1-hydroxypropyl)indoline



A 3 M solution (1.4 ml) of ethylmagnesium in ether was added dropwise at -78°C into a solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-formylindoline (1.0 g) in tetrahydrofuran (30 ml) and the resultant mixture was allowed to warm to room temperature. Then a saturated aqueous solution of ammonium chloride and ethyl acetate were added to the reaction solution and the layers were separated. The organic layer was washed with brine and dried over magnesium sulfate. After removing the solvent, the residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (710 mg) as a colorless oil (yield: 66%) .

To a solution of this oil (200 mg) in acetone, oxalic acid (47 mg) was added to give the oxalate (150 mg) of the title compound as a pale brown powder.

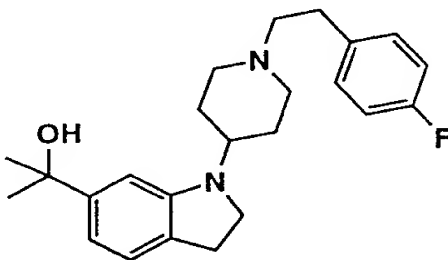
m.p. (oxalate): 106 - 108°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 0.80 (3H, t, J=7Hz), 1.50-1.61 (2H, m), 1.80-1.95 (4H, m), 2.85 (2H, t, J=8Hz), 2.95-3.25 (6H, m), 3.31 (2H, t, J=8Hz), 3.51-3.62 (2H, m), 3.66-3.78 (1H, m), 4.32 (1H, t, J=6Hz), 6.49-6.51 (2H, m), 6.94 (1H, d, J=8Hz), 7.16-7.21 (2H, m), 7.31-7.35 (2H, m).

FAB-Mass: 383 (MH⁺).

Example 139: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(1-hydroxy-1-methylethyl)indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-bromoindoline (0.75 g), a 2.5 M solution (1.1 ml) of n-butyllithium in hexane and acetone (0.16 g) were treated as in Example 130 to give the oxalate (250 mg) of the title compound as a pale yellow powder (yield: 35%).

m.p. (oxalate): 179 - 182°C.

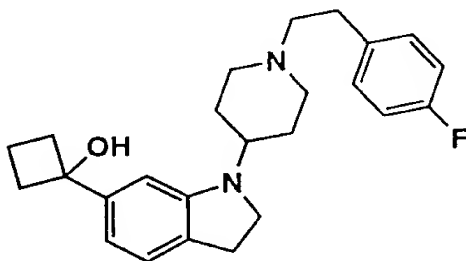
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.38 (6H, s), 1.81-1.90 (4H, m), 2.83 (2H, t, J=8Hz), 2.91-3.04 (4H, m), 3.11-3.20 (2H, m), 3.30 (2H, t, J=8Hz), 3.50-3.59 (2H, m), 3.66-3.74 (1H, m), 6.63-6.65 (2H, m), 6.92 (1H,

d, J=8Hz), 7.15-7.20 (2H, m), 7.31-7.35 (2H, m).

FAB-Mass: 383 (MH+).

Example 140: Synthesis of 1-[1-(4-fluorophenethyl)-
piperidin-4-yl]-6-(1-hydroxycyclobutyl)indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-bromoindoline (0.5 g), a 2.5 M solution (0.8 ml) of n-butyllithium in hexane and cyclobutanone (0.14 ml) were treated as in Example 130 to give the hydrochloride (150 mg) of the title compound as a white powder (yield: 29%).

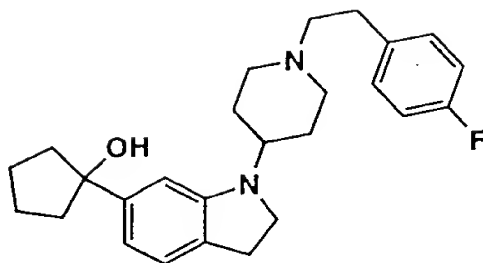
m.p. (hydrochloride): 172 - 175°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.53-1.64 (1H, m), 1.82-1.94 (3H, m), 1.96-2.09 (2H, m), 2.16-2.26 (2H, m), 2.31-2.40 (2H, m), 2.87 (2H, t, J=8Hz), 3.00-3.44 (9H, m), 3.60-3.70 (2H, m), 6.64 (1H, s), 6.72 (1H, d, J=8Hz), 6.99 (1H, d, J=8Hz), 7.16-7.22 (2H, m), 7.32-7.36 (2H, m).

FAB-Mass: 395 (MH+).

Example 141: Synthesis of 1-[1-(4-fluorophenethyl)-
piperidin-4-yl]-6-(1-hydroxycyclopentyl)indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-bromoindoline (0.5 g), a 2.5 M solution (0.8 ml) of n-butyllithium in hexane and cyclopentanone (0.17 ml) were treated as in Example 130 to give the hydrochloride (240 mg) of the title compound as a white powder (yield: 45%).

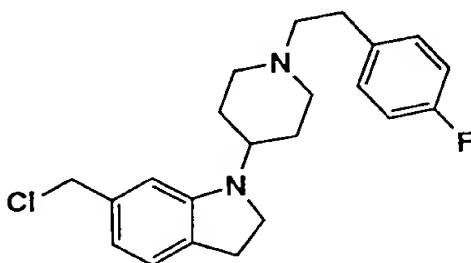
m.p. (hydrochloride): 191 - 194°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.64-2.00 (12H, m), 2.81 (2H, t, J=8Hz), 2.96-3.04 (2H, m), 3.06-3.16 (2H, m), 3.20-3.31 (2H, m), 3.34-3.78 (5H, m), 6.59 (1H, s), 6.64 (1H, d, J=8Hz), 6.90 (1H, d, J=8Hz), 7.11-7.19 (2H, m), 7.30-7.38 (2H, m).

FAB-Mass: 409 (MH⁺).

Example 142: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-chloromethylindoline

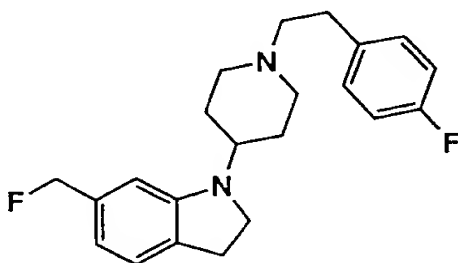


Conc. hydrochloric acid (280 ml) was added to 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-hydroxymethylindoline (about 70 g) and the resultant mixture was stirred at 80°C for a day. Under ice cooling, the reaction solution was neutralized with a conc. aqueous solution of sodium hydroxide followed by addition of ethyl acetate (200 ml). The resulting crystals were collected by filtration and dissolved in ethyl acetate (500 ml) and a 5 N aqueous solution (500 ml) of sodium hydroxide and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound (70 g) as a pale yellow powder (yield: 94%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.76-1.90 (4H, m), 2.10-2.26 (2H, m), 2.58-2.70 (2H, m), 2.78-2.90 (2H, m), 2.94 (2H, t, J=8Hz), 3.10-3.24 (2H, m), 3.36-3.51 (1H, m), 3.43 (2H, t, J=8Hz), 4.53 (2H, s), 6.40 (1H, s), 6.60 (1H, d, J=8Hz), 6.95-7.02 (3H, m), 7.14-7.19 (2H, m).

Example 143: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-fluoromethylindoline



Diethylaminosulfatetrifluoride (DAST, 160 mg) was added dropwise at -78°C into a solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-hydroxymethylindoline (300 mg) in methylene chloride (10 ml) and the resultant mixture was stirred for 1 hr. Then a saturated aqueous solution of sodium bicarbonate and ethyl acetate were added thereto and the layers were separated. The organic layer was dried over anhydrous magnesium sulfate and the obtained residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) followed by conversion into a hydrochloride in a conventional manner to give the hydrochloride (100 mg) of the title compound as a white powder (yield: 30%).

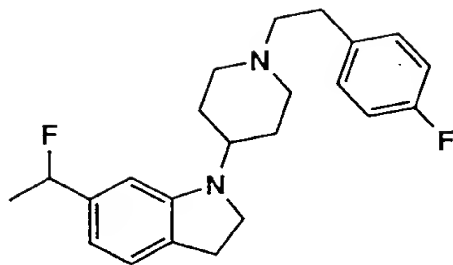
m.p. (hydrochloride): 190°C (decomp.).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.84-1.93 (2H, m), 2.01-2.14 (2H, m), 2.87-2.95 (2H, m), 3.00-3.16 (4H, m), 3.21-3.30 (4H, m), 3.37 (2H, t, J=8Hz), 3.59-3.68 (2H, m), 3.73-3.83 (1H, m), 5.28 (2H, d, J=22Hz), 6.60-6.63 (2H, m), 7.05 (1H, d, J=8Hz), 7.16-7.21 (2H, m), 7.33-7.36 (2H, m), 10.70 (1H, br-s).

FAB-Mass: 357 (MH+).

Example 144: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1-fluoroethyl)indoline



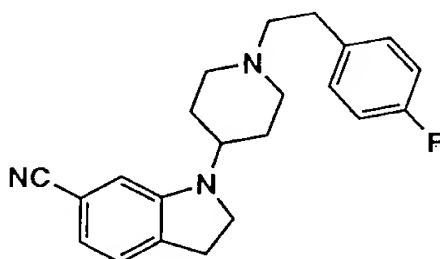
Diethylaminosulfatetrifluoride (DAST, 220 mg) was added dropwise at -78°C into a solution (20 ml) of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1-hydroxyethyl)indoline (400 mg) in methylene chloride and the resultant mixture was stirred for 1 hr. Then a saturated aqueous solution of sodium bicarbonate and chloroform were added thereto and the layers were separated. The organic layer was dried over anhydrous magnesium sulfate and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system) followed by conversion into a hydrochloride in a conventional manner to give the hydrochloride (100 mg) of the title compound as a white hygroscopic amorphous solid (yield: 23%).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO}-d_6$):

$\delta(\text{ppm})$ 1.55(3H, dd, $J=24, 6\text{Hz}$), 1.82-1.92(2H, m), 1.96-2.10(2H, m), 2.81-2.93(2H, m), 3.01-3.18(4H, m), 3.22-3.49(4H, m), 3.59-3.69(2H, m), 3.71-3.85(1H, m), 5.57(1H, dq, $J=48, 6\text{Hz}$), 6.54-6.61(2H, m), 6.98-7.04(1H, m), 7.18-7.21(2H, m), 7.32-7.40(2H, m).

FAB-Mass: 371(MH+).

Example 145: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-cyanomethylindoline



Dimethyl sulfoxide (500 ml) and sodium cyanide (9.8 g) were added to 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-chloromethylindoline (about 70 g) and the resultant mixture was stirred at 50°C for 2 hr. Next, ice water (500 ml) was added to the reaction solution followed by vigorously stirring. The resulting crystals were collected by filtration, washed with water and air-dried at 80°C to give the title compound (67 g) as a pale yellow powder (yield: 93%).

A portion of this product was purified by silica gel column chromatography (ethyl acetate/hexane system) followed by conversion into a hydrochloride in a conventional manner to give the hydrochloride of the title compound as a white powder.
m.p. (hydrochloride): 211 - 214°C.

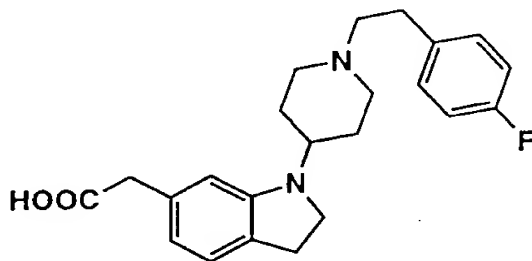
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.83-1.91(2H, m), 1.99-2.12(2H, m), 2.90(2H, t, J=8Hz), 3.00-3.19(4H, m), 3.21-3.32(2H, m), 3.35(2H, t, J=8Hz), 3.60-3.80(3H, m), 3.90(2H, s), 6.49(1H, s), 6.51(1H, d, J=8Hz),

7.01 (1H, d, J=8Hz), 7.13-7.21 (2H, m), 7.30-7.40 (2H, m).

FAB-Mass: 364 (MH+).

Example 146: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-cyanomethylindoline (about 67 g) was dissolved in water (134 ml) and conc. sulfuric acid (134 ml) and the resultant solution was heated under reflux for 7 hr. Under ice cooling, the pH value of the reaction mixture was adjusted to 10 with a conc. aqueous solution of sodium hydroxide. Then ethyl acetate (300 ml) was added thereto followed by vigorous stirring. After adjusting the pH value of the resultant mixture to about 6 with conc. hydrochloric acid, the resulting crystalline precipitates were collected by filtration, washed with water and air-dried at 50°C over day and night to give the title compound (58 g) as a white powder (yield: 76%).

m.p.: 130 - 132°C.

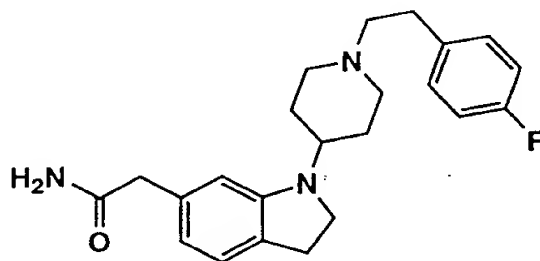
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.53-1.73 (4H, m), 2.70-2.90 (4H, m), 3.00-3.53 (12H,

m), 6.31(1H, s), 6.39(1H, d, J=8Hz), 6.90(1H, d, J=8Hz),
7.04-7.15(2H, m), 7.22-7.30(2H, m).

FAB-Mass: 383 (MH+).

Example 147: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-
fluorophenethyl)piperidin-4-yl]-6-carbamoylmethylindoline



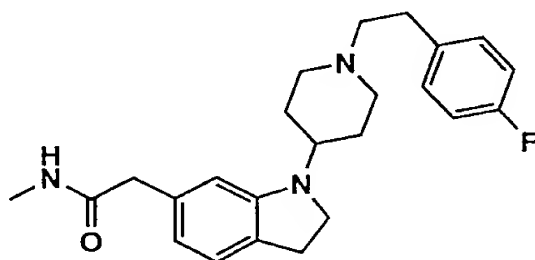
Crude 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-cyanomethylindoline (230 mg) was dissolved in conc. sulfuric acid (5 ml) and the resultant solution was stirred overnight. The reaction solution was diluted with ice water and the pH value thereof was adjusted to 10 under ice cooling with a conc. aqueous solution of sodium hydroxide. After extracting the reaction solution with ethyl acetate, the organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/ethanol system) followed by conversion into a hydrochloride in a conventional manner to give the hydrochloride (200 mg) of the title compound as a white hygroscopic amorphous solid (yield: 76%).

¹H-NMR (400 MHz, DMSO-d₆):

δ (ppm) 1.83-1.92 (2H, m), 2.02-2.17 (2H, m), 2.86 (2H, t, J=8Hz), 3.00-3.16 (4H, m), 3.21-3.29 (2H, m), 3.34 (2H, t, J=8Hz), 3.60-4.10 (5H, m), 6.43-6.51 (2H, m), 6.81 (1H, br-s), 6.95 (1H, d, J=8Hz), 7.16-7.21 (2H, m), 7.32-7.39 (3H, m).

FAB-Mass: 382 (MH+).

Example 148: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(methylcarbamoylmethyl)indoline



Ethyl chlorocarbonate (87 mg) was added at -78°C to a mixture of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (250 mg), triethylamine (81 mg), dimethylformamide (6 ml) and tetrahydrofuran (8 ml). After heating the resultant mixture to -30°C , a 2 N solution (0.4 ml) of methylamine in tetrahydrofuran was added thereto. The resultant mixture was further warmed to room temperature and stirred for additional 30 min. Ice water and ethyl acetate were added to the liquid reaction mixture and the layers were separated. The organic layer was washed successively with water, a saturated aqueous solution of sodium bicarbonate and brine, dried over anhydrous magnesium sulfate and concentrated

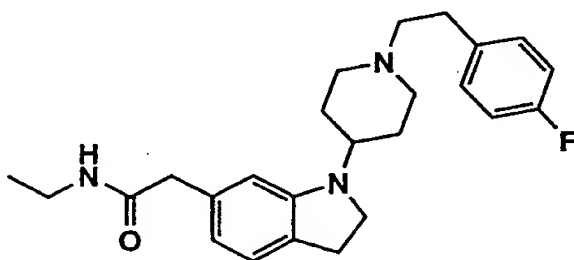
under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/ethanol system) followed by conversion into a hydrochloride in a conventional manner to give the hydrochloride (120 mg) of the title compound as a white hygroscopic amorphous substance (yield: 45%).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.83-1.92(2H, m), 2.00-2.13(2H, m), 2.55(3H, d, J=4Hz), 2.86(2H, t, J=8Hz), 2.99-3.16(4H, m), 3.22-3.30(4H, m), 3.33(2H, t, J=8Hz), 3.60-3.76(3H, m), 6.45-6.50(2H, m), 6.94(1H, d, J=8Hz), 7.16-7.22(2H, m), 7.32-7.40(2H, m), 7.84(1H, d, J=4Hz), 10.53(1H, br-s).

FAB-Mass: 396(MH+).

Example 149: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(ethylcarbamoylmethyl)indoline



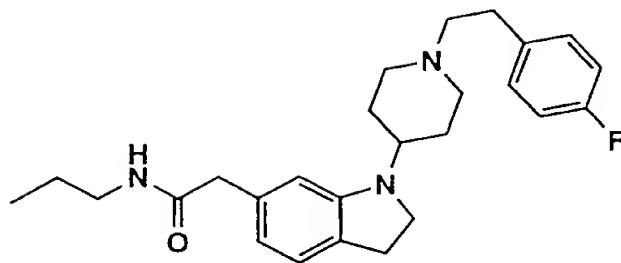
Under ice cooling, 1,1'-carbonyldiimidazole (1.0 g) was added to a solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (2.0 g) in dimethylformamide (40 ml). After stirring the mixture for 2 hr, ethylamine hydrochloride (0.51 g) was added thereto. Then the resultant

mixture was allowed to warm to room temperature and stirred for additional 5 hr. A saturated aqueous solution of sodium bicarbonate and ethyl acetate were added to the reaction solution and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Then the residue was dissolved in hot toluene (10 ml). After allowing to cool to room temperature, the resulting crystals were collected by filtration to give the title compound (1.3 g) as a white powder (yield: 56%).

Next, the product was converted into a hydrochloride in a conventional manner followed by recrystallization from acetone to give the hydrochloride of the title compound as a white powder.

 $^1\text{H-NMR}$ (400 MHz, DMSO- d_6):

FAB-Mass: 410 (MH⁺) .



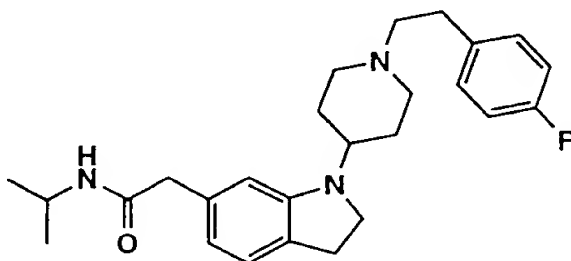
1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (220 mg), 1,1'-carbonyldiimidazole (110 mg) and n-propylamine (41 mg) were treated as in Example 149 to give the title compound (90 mg) as white needles (yield: 37%). m.p.: 143 - 145°C.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 0.83 (3H, t, J=7Hz), 1.42 (2H, sextet, J=7Hz), 1.75-1.79 (4H, m), 2.10-2.30 (2H, m), 2.53-2.71 (2H, m), 2.78-2.90 (2H, m), 2.95 (2H, t, J=8Hz), 3.09-3.21 (4H, m), 3.37-3.49 (1H, m), 3.42 (2H, t, J=8Hz), 3.50 (2H, s), 5.51 (1H, br-s), 6.29 (1H, s), 6.48 (1H, d, J=8Hz), 6.92-7.01 (3H, m), 7.12-7.20 (2H, m).

FAB-Mass: 424 (MH⁺).

Example 151: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(isopropylcarbamoylmethyl)indoline



Under ice cooling, 1,1'-carbonyldimidazole (15 g) was added to a solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (30 g) in dimethylformamide (240 ml) and the resultant mixture was stirred for 2 hr. After adding isopropylamine (5.6 g), the mixture was warmed to room temperature and then stirred for additional 2 hr. Next, ice water (240 ml) and ethyl acetate (300 ml) were added to the reaction solution and the layers were separated. The organic layer was washed successively with water, a saturated aqueous solution of sodium bicarbonate and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in hot ethyl acetate (80 ml). After allowing to cool to room temperature, the resulting crystals were collected by filtration to give the title compound (17.2 g) as a white powder (yield: 52%).

Next, the product was converted into a hydrochloride in a conventional manner followed by recrystallization from ethanol to give the hydrochloride of the title compound as a white powder.

m.p. (hydrochloride): 153 - 155°C.

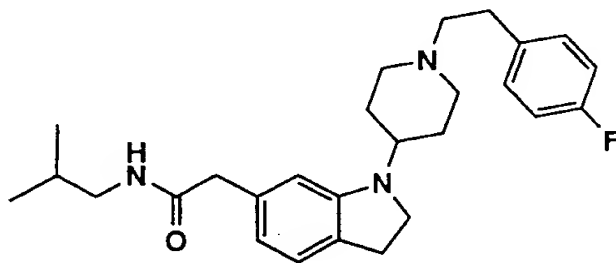
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.03 (6H, d, J=7Hz), 1.84-1.92 (2H, m), 1.96-2.10 (2H, m), 2.85 (2H, t, J=8Hz), 3.01-3.16 (4H, m), 3.20-3.38 (6H, m), 3.61-3.83 (4H, m), 6.42-6.46 (2H, m), 6.93 (1H, d, J=8Hz),

7.16-7.23(2H, m), 7.31-7.38(2H, m), 7.83(1H, d, J=8Hz).

FAB-Mass: 424(MH+).

Example 152: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(isobutylcarbamoylmethyl)indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (300 mg), 1,1'-carbonyldiimidazole (150 mg) and isobutylamine (69 mg) were treated as in Example 151 to give the hydrochloride (270 mg) of the title compound as white needles (yield: 72%).

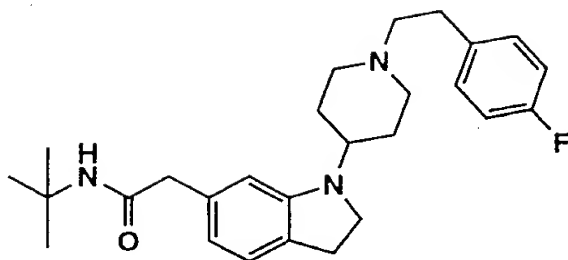
m.p. (hydrochloride): 122 - 124°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 0.81(6H, d, J=7Hz), 1.66(1H, septet, J=7Hz), 1.84-1.92(2H, m), 2.00-2.15(4H, m), 2.81-2.90(4H, m), 3.02-3.15(2H, m), 3.23-3.38(4H, m), 3.44-3.73(5H, m), 6.48-6.53(2H, m), 6.95(1H, d, J=8Hz), 7.17-7.22(2H, m), 7.29-7.40(2H, m), 7.94(1H, br-s).

FAB-Mass: 438(MH+).

Example 153: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(t-butylcarbamoylmethyl)indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (250 mg), 1,1'-carbonyldiimidazole (130 mg) and t-butylamine (58 mg) were treated as in Example-151 to give the hydrochloride (140 mg) of the title compound as a pale brown powder (yield: 45%).

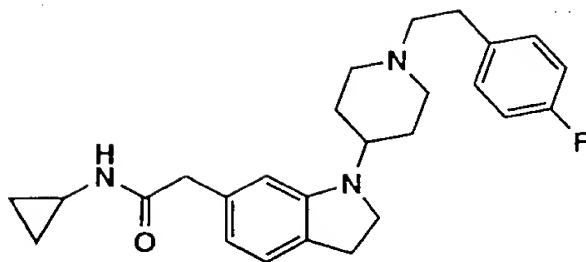
m.p. (hydrochloride): 189 - 192°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.24(9H, s), 1.84-1.92(2H, m), 2.03-2.16(2H, m), 2.87(2H, t, J=8Hz), 3.03-3.15(4H, m), 3.22-3.30(4H, m), 3.34(2H, t, J=8Hz), 3.58-3.77(3H, m), 6.47-6.50(2H, m), 6.95(1H, d, J=8Hz), 7.16-7.21(2H, m), 7.32-7.36(2H, m), 7.58(1H, br-s), 10.69(1H, br-s).

FAB-Mass: 438(MH⁺).

Example 154: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(cyclopropylcarbamoylmethyl)indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (250 mg), 1,1'-carbonyldiimidazole (130 mg) and cyclopropylamine (45 mg) were treated as in Example 151 to give the title compound (110 mg) as a white powder (yield: 40%).

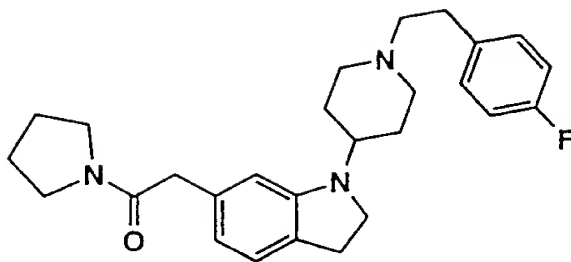
m.p.: 182 - 184°C.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 0.36-0.41(2H, m), 0.69-0.74(2H, m), 1.75-1.90(4H, m), 2.10-2.30(2H, m), 2.60-2.71(3H, m), 2.75-2.90(2H, m), 2.94(2H, t, J=8Hz), 3.10-3.25(2H, m), 3.35-3.48(5H, m), 5.60(1H, br-s), 6.26(1H, s), 6.42(1H, d, J=8Hz), 6.96-7.01(3H, m), 7.15-7.20(2H, m).

FAB-Mass: 422(MH+).

Example 155: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(tetramethylenecarbamoylmethyl)indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (360 mg), 1,1'-carbonyldiimidazole (160 mg) and pyrrolidine (70 mg) were treated as in Example-151 to give the hydrochloride (280 mg) of the title compound as a white powder (yield: 60%).

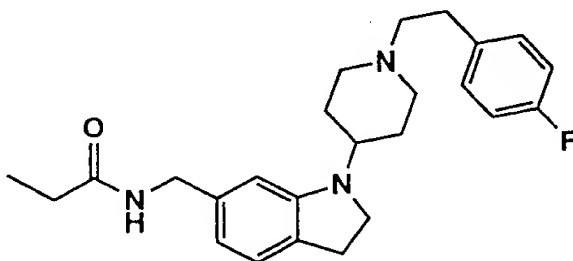
m.p. (hydrochloride): 159 - 161°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.90-2.04(8H, m), 2.86(2H, t, J=8Hz), 3.00-3.19(4H, m), 3.21-3.39(6H, m), 3.42(2H, t, J=8Hz), 3.61-3.76(3H, m), 6.41(1H, s), 6.43(1H, d, J=8Hz), 6.94(1H, d, J=8Hz), 7.17-7.22(2H, m), 7.30-7.37(2H, m).

FAB-Mass: 436(MH⁺).

Example 156: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-propionylaminomethylindoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-aminomethylindoline (200 mg), triethylamine (69 mg) and propionyl chloride (63 mg) were treated as in Example 133 to give the hydrochloride (88 mg) of the title compound as a pale brown powder (yield: 35%).

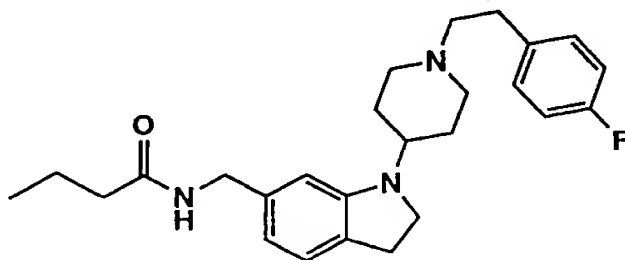
m.p. (hydrochloride): 157°C (decomp.).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 0.99(3H, t, J=7Hz), 1.82-2.10(4H, m), 2.10(2H, q, J=7Hz), 2.84(2H, t, J=8Hz), 2.92-3.14(4H, m), 3.21-3.35(4H, m), 3.59-3.73(3H, m), 4.12(2H, d, J=6Hz), 6.41(1H, s), 6.44(1H, d, J=8Hz), 6.94(1H, d, J=8Hz), 7.15-7.20(2H, m), 7.30-7.35(2H, m), 8.12(1H, t, J=6Hz).

FAB-Mass: 410(MH+).

Example 157: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(n-butyryl)aminomethylindoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-aminomethylindoline (200 mg), triethylamine (69 mg) and n-butyryl chloride (72 mg) were treated as in Example 133 to give the title compound (110 mg) as pale yellow needles (yield: 46%).

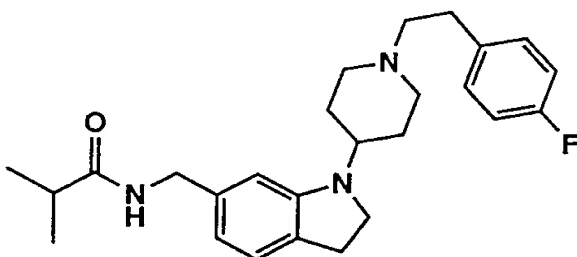
m.p.: 153 - 155°C.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 0.96(3H, t, J=7Hz), 1.68(2H, sextet, J=7Hz), 1.75-1.83(4H, m), 2.10-2.22(2H, m), 2.17(2H, q, J=7Hz), 2.55-2.70(2H, m), 2.74-2.90(2H, m), 2.93(2H, t, J=8Hz), 3.05-3.20(2H, m), 3.35-3.45(1H, m), 3.42(2H, t, J=8Hz), 4.34(2H, d, J=6Hz), 6.33(1H, s), 6.50(1H, d, J=8Hz), 6.95-7.00(3H, m), 7.10-7.19(2H, m).

FAB-Mass: 424(MH⁺).

Example 158: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-isobutyrylaminomethylindoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-aminomethylindoline (300 mg), triethylamine (80 mg) and isobutyryl chloride (90 mg) were treated as in Example 133 to give the title compound (200 mg) as white needles (yield: 58%).
m.p.: 163 - 165°C.

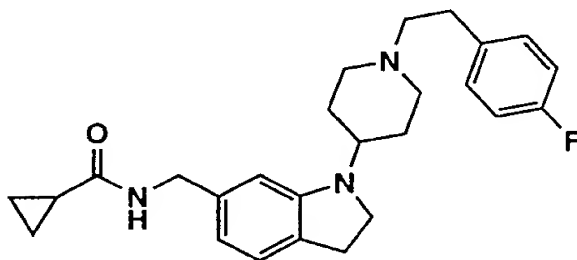
¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.17(6H, d, J=7Hz), 1.51-1.66(2H, m), 1.75-1.87(2H, m), 2.10-2.25(2H, m), 2.36(1H, septet, J=7Hz), 2.56-2.72(2H, m),

m), 2.75-2.95(2H, m), 2.93(2H, t, J=8Hz), 3.08-3.25(2H, m), 3.35-3.45(1H, m), 3.42(2H, t, J=8Hz), 4.34(2H, d, J=6Hz), 6.33(1H, s), 6.50(1H, d, J=8Hz), 6.96-7.01(3H, m), 7.15-7.19(2H, m).

FAB-Mass: 424(MH+).

Example 159: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-cyclopropanecarboxamindomethylindoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-aminomethylindoline (250 mg) and cyclopropanecarbonyl chloride (81 mg) were treated as in Example 133 to give the hydrochloride (100 mg) of the title compound as a white powder (yield: 31%).

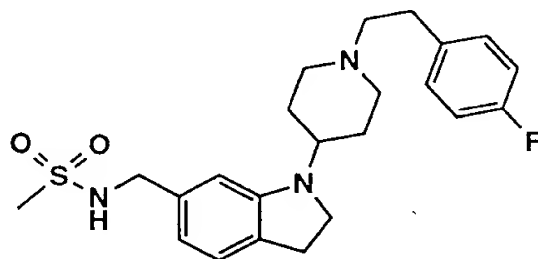
m.p.: 143 - 146°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 0.60-0.69(4H, m), 1.55-1.63(1H, m), 1.83-1.90(2H, m), 1.99-2.09(2H, m), 2.86(2H, t, J=8Hz), 3.02-3.16(4H, m), 3.22-3.30(2H, m), 3.31(2H, t, J=8Hz), 3.60-3.79(3H, m), 4.16(2H, d, J=6Hz), 6.47(1H, s), 6.48(1H, d, J=8Hz), 6.98(1H, d, J=8Hz), 7.16-7.21(2H, m), 7.32-7.38(2H, m), 8.43(1H, d, J=6Hz).

FAB-Mass: 422(MH+).

Example 160: Synthesis of 1-[1-(4-fluorophenethyl)-
piperidin-4-yl]-6-methylsulfonylaminomethylindoline



Under ice cooling, methanesulfonyl chloride (78 mg) was added dropwise into a solution of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-aminomethylindoline (200 mg) in pyridine (20 ml) and the resultant mixture was stirred for 30 min. After concentrating under reduced pressure, the residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Then the residue was purified by silica gel column chromatography (ethyl acetate/ethanol system) followed by conversion into a hydrochloride in a conventional manner to give the hydrochloride (160 mg) of the title compound as a white hygroscopic amorphous solid (yield: 60%).

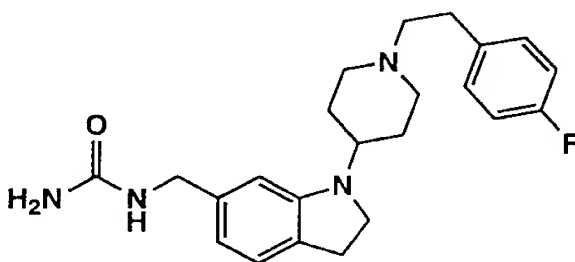
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.81-1.91(2H, m), 2.00-2.12(2H, m), 2.78(3H, s), 2.82-2.90(2H, m), 2.97-3.15(4H, m), 3.19-3.30(2H, m), 3.33(2H,

t, J=8Hz), 3.58-3.75(3H, m), 4.02(2H, s), 6.53(1H, s), 6.55(1H, d, J=8Hz), 6.98(1H, d, J=8Hz), 7.14-7.19(2H, m), 7.30-7.34(2H, m), 7.42(1H, br-s), 10.70(1H, br-s).

FAB-Mass: 432(MH+).

Example 161: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-ureidomethylindoline



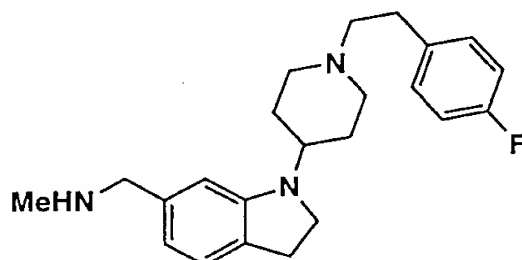
A solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminomethylindoline (300 mg) and nitrourea (90 mg) in methanol (10 ml) was heated under reflux for 3 hr. After concentrating under reduced pressure, the residue was crystallized from ethyl acetate. The resulting crystals were dissolved in ethanol followed by conversion into a hydrochloride to give the hydrochloride (260 mg) of the title compound as a gray hygroscopic amorphous solid (yield: 71%).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.83-2.02(4H, m), 2.84(2H, t, J=8Hz), 2.98-3.16(4H, m), 3.20-3.74(7H, m), 4.04(2H, br-s), 6.42(1H, s), 6.45(1H, d, J=8Hz), 6.94(1H, d, J=8Hz), 7.15-7.20(2H, m), 7.31-7.34(2H, m).

FAB-Mass: 397(MH+).

Example 162: Synthesis of 1-[1-(4-fluorophenethyl)-
piperidin-4-yl]-6-N-methylaminomethylindoline



Ethyl chlorocarbonate (300 mg) was added dropwise at room temperature into a solution of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-aminomethylindoline (800 mg) and triethylamine (290 mg) in methylene chloride (20 ml) and the resultant mixture was stirred for 90 min. After concentrating under reduced pressure, the residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was then added to a suspension of lithium aluminum hydride (260 mg) in tetrahydrofuran (20 ml) and the resultant mixture was heated under reflux for 1 hr. Under ice water cooling, water (0.26 ml), a 5 N aqueous solution (0.78 ml) of sodium hydroxide and further water (0.26 ml) were carefully added dropwise to the reaction solution followed by vigorous stirring. The resulting precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified

by NH-silica gel column chromatography (ethyl acetate/ethanol system) to give the title compound (700 mg) as an oil (yield: 83%).

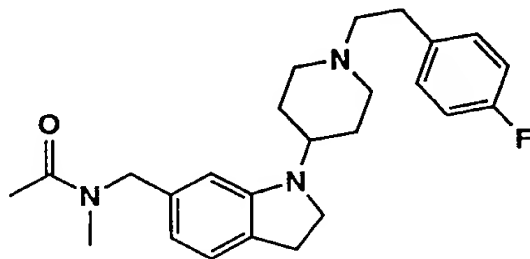
A portion of this product was converted into a hydrochloride in a conventional manner to give the hydrochloride of the title compound as a dark red hygroscopic amorphous solid.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.90-1.98(2H, m), 2.06-2.20(2H, m), 2.48(3H, s), 2.89(2H, t, J=8Hz), 2.99-3.12(4H, m), 3.22-3.31(2H, m), 3.35(2H, t, J=8Hz), 3.58-3.68(3H, m), 3.95(2H, br-s), 6.64(1H, d, J=8Hz), 6.87(1H, s), 7.03(1H, d, J=8Hz), 7.10-7.19(2H, m), 7.30-7.34(2H, m), 9.22(2H, br-s), 10.79(1H, br-s).

FAB-Mass: 368(MH⁺).

Example 163: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-N-methylacetamidomethylindoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-N-methylaminomethylindoline (540 mg), triethylamine (200 mg) and acetyl chloride (150 mg) were treated as in Example 133 to give

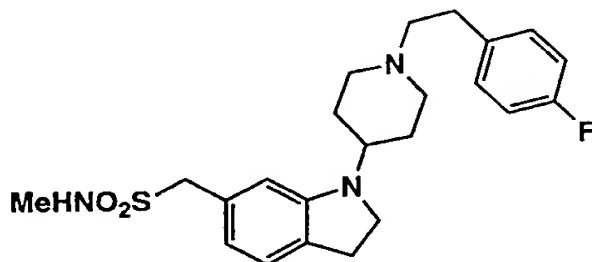
the hydrochloride (330 mg) of the title compound as a white hygroscopic amorphous solid (yield: 50%).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.81-1.89(2H, m), 1.92-2.06(2H, m), 2.02(3H, s), 2.75(1.5H, s), 2.85(1.5H, s), 2.80-2.90(2H, m), 3.00-3.14(4H, m), 3.21-3.36(4H, m), 3.58-3.73(3H, m), 4.35(1H, s), 4.40(1H, s), 6.32(0.5H, s), 6.36(0.5H, s), 6.37(0.5H, d, J=8Hz), 6.40(0.5H, d, J=8Hz), 6.95(0.5H, d, J=8Hz), 6.99(0.5H, d, J=8Hz), 7.14-7.19(2H, m), 7.30-7.34(2H, m).

FAB-Mass: 410(MH+).

Example 164: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(N-methylsulfamoylmethyl)indoline



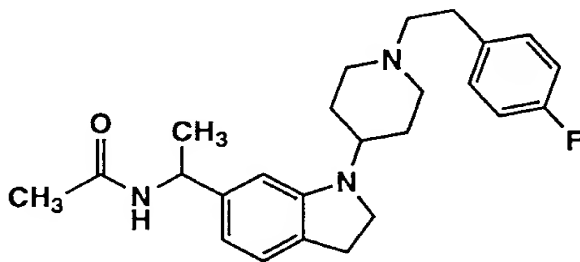
6-(N-Methylsulfamoylmethyl)indoline (100 mg), 1-(4-fluorophenethyl)-4-piperidone (150 mg), acetic acid (120 mg) and triacetoxylated sodium borohydride (140 mg) were treated as in Example 1 to give the title compound (100 mg) as white prisms (yield: 53%).

m.p.: 162 - 164°C.

¹H-NMR (400 MHz, CDCl₃):

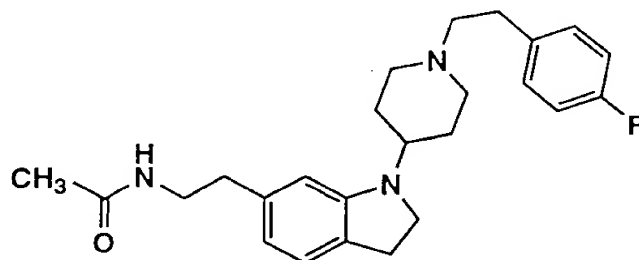
[illegible]

Example 165: Synthesis of 1-[1-(4-fluorophenethyl)-
piperidin-4-yl]-6-(1-acetamidoethyl)indoline

 $^1\text{H-NMR}$ (400 MHz, DMSO-d_6):

FAB-Mass: 410 (MH⁺).

Example 166: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindoline



A mixture of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-cyanomethylindoline (0.25 g), platinum oxide (50 mg), 5 N hydrochloric acid (1.0 ml) and methanol (20 ml) was catalytically reduced under hydrogen atmosphere of 3 atm. After 4 hr, the catalyst was filtered off and the filtrate was concentrated under reduced pressure. To the resulting residue were added a 5 N aqueous solution (10 ml) of sodium hydroxide, acetyl chloride (0.2 ml) and methylene chloride (20 ml) and the resultant mixture was stirred vigorously for 1 hr. Next, it was diluted with water and chloroform and the layers were separated. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) followed by conversion into an oxalate in a conventional manner to give the oxalate (90 mg) of the title compound as a brown hygroscopic amorphous solid (yield: 26%).

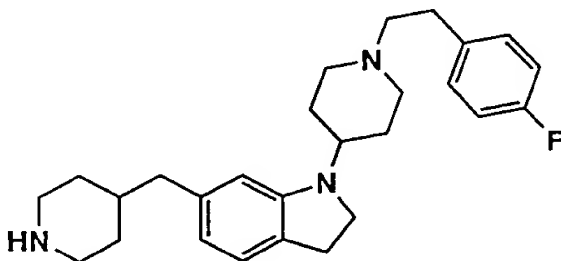
¹H-NMR (400 MHz, DMSO-d₆):

09640639-030201
T0000-00000000

δ (ppm) 1.80-1.94(4H, m), 2.08(3H, s), 2.58(2H, t, J=7Hz), 2.84(2H, t, J=8Hz), 2.93-3.07(4H, m), 3.15-3.24(4H, m), 3.31(2H, t, J=8Hz), 3.51-3.59(2H, m), 3.64-3.74(1H, m), 6.36(1H, s), 6.39(1H, d, J=8Hz), 7.15-7.21(2H, m), 7.31-7.39(2H, m), 7.88(1H, t, J=6Hz).

FAB-Mass: 410(MH+).

Example 167: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[(piperidin-4-yl)methyl]indoline



A mixture of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1'-hydroxy-4-pyridylmethyl)indoline (1.2 g), 10% palladium-carbon (600 mg), 5 N hydrochloric acid (2.9 ml) and ethanol (30 ml) was catalytically reduced under hydrogen atmosphere of 3 atm. After 7 hr, platinum oxide (150 mg) was added thereto and the catalytic reduction was continued for additional 2 hr. Then the catalyst was filtered off and the filtrate was concentrated under reduced pressure. The resulting residue was diluted with a saturated aqueous solution of sodium bicarbonate and ethyl acetate and the layers were separated. The organic layer was washed with brine and dried

over anhydrous magnesium sulfate. The residue was purified by NH-silica gel column chromatography (ethanol/ethyl acetate system) followed by conversion into a hydrochloride in a conventional manner to give the hydrochloride (510 mg) of the title compound as a white powder (yield: 33%).

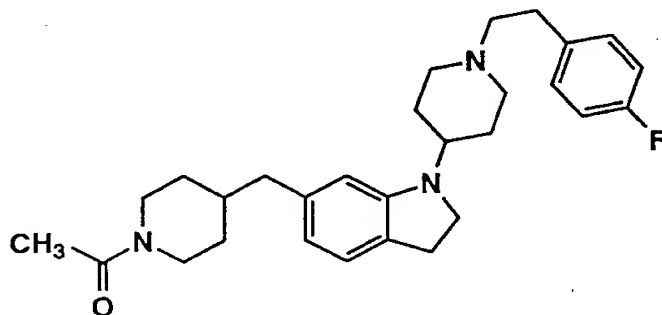
m.p. (hydrochloride): 162 - 165°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.27-1.40(2H, m), 1.65-1.91(5H, m), 2.03-2.17(2H, m), 2.38-2.44(2H, m), 2.51-2.84(2H, m), 2.84(2H, t, J=8Hz), 3.01-3.45(10H, m), 3.59-3.76(3H, m), 3.36-3.39(2H, m), 6.93(1H, d, J=8Hz), 7.16-7.21(2H, m), 7.32-7.36(2H, m), 8.68(1H, br-s), 8.85(1H, br-s), 10.79(1H, br-s).

FAB-Mass: 422(MH+).

Example 168: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[(1-acetylpiperidin-4-yl)methyl]indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-

[(piperidin-4-yl)methyl]indoline (100 mg) and acetyl chloride (0.1 ml) were treated as in Example 133 to give the hydrochloride (50 mg) of the title compound as a pale yellow hygroscopic

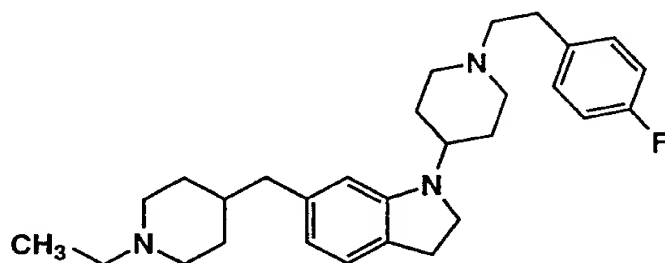
amorphous solid (yield: 45%).

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6):

$\delta(\text{ppm})$ 0.87-1.12(2H, m), 1.50-1.78(3H, m), 1.82-1.91(2H, m), 1.96(3H, s), 2.00-2.16(2H, m), 2.36-2.45(2H, m), 2.81-2.98(4H, m), 3.00-3.16(4H, m), 3.20-3.38(4H, m), 3.57-3.80(4H, m), 4.26-4.36(1H, m), 6.40-6.42(2H, m), 6.94(1H, d, $J=8\text{Hz}$), 7.16-7.21(2H, m), 7.32-7.36(2H, m).

FAB-Mass: 464(MH+).

Example 169: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[(1-ethylpiperidin-4-yl)methyl]indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-[(piperidin-4-yl)methyl]indoline (190 mg) and ethyl iodide (84 mg) were treated as in Example 2 to give the hydrochloride (50 mg) of the title compound as a pale brown hygroscopic amorphous solid (yield: 21%).

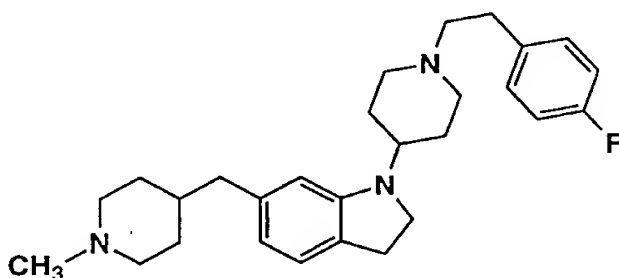
$^1\text{H-NMR}$ (400 MHz, DMSO-d_6):

$\delta(\text{ppm})$ 1.22(3H, t, $J=7\text{Hz}$), 1.43-1.56(2H, m), 1.68-1.70(5H, m), 2.04-2.19(2H, m), 2.38-2.45(2H, m), 2.69-2.83(2H, m), 2.85(2H, t, $J=8\text{Hz}$), 2.95-3.18(6H, m), 3.20-3.31(2H, m), 3.32(2H,

t, J=8Hz), 3.35-3.43(2H, m), 3.57-3.70(3H, m), 6.37-6.41(2H, m), 6.94(1H, d, J=8Hz), 7.16-7.22(2H, m), 7.30-7.37(2H, m), 10.17(1H, br-s), 10.80(1H, br-s).

FAB-Mass: 450(MH+).

Example 170: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[(1-methylpiperidin-4-yl)methyl]indoline



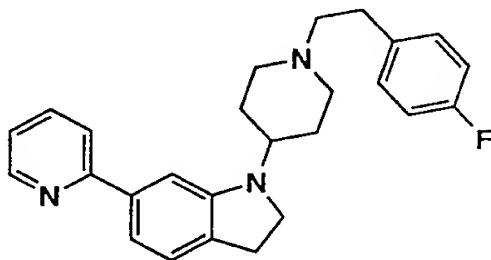
A mixture of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[(piperidin-4-yl)methyl]indoline (200 mg), formamide (40 mg), formic acid (44 mg), water (5 ml) and methanol (5 ml) was heated under reflux overnight. Then, a saturated aqueous solution of sodium bicarbonate and ethyl acetate were added thereto and the layers were separated. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. Then the residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) followed by conversion into a hydrochloride in a conventional manner to give the hydrochloride (60 mg) of the title compound as a pale yellow hygroscopic amorphous solid (yield: 25%).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.40-1.54(2H, m), 1.63-1.76(3H, m), 1.82-1.90(2H, m), 2.05-2.18(2H, m), 2.38-2.44(2H, m), 2.51(3H, s), 2.64-2.65(2H, m), 2.80-2.90(2H, m), 3.01-3.17(4H, m), 3.20-3.39(6H, m), 3.58-3.70(3H, m), 6.38-6.42(2H, m), 6.94(1H, d, J=8Hz), 7.16-7.21(2H, m), 7.32-7.36(2H, m), 10.34(1H, br-s), 10.85(1H, br-s).

FAB-Mass: 436(MH+).

Example 171: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-pyridyl)indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-bromoindoline (0.405 g) and 2-tributylstannylpyridine (1.85 g) synthesized in accordance with the method described in Tetrahedron Lett., 4407 (1986). were treated as in Production Example 13-2 to give the title compound (0.234 g) as a pale yellow oil (yield: 46.6%).

Next, oxalic acid (52 mg) was added to the above product to give an oxalate followed by recrystallization from acetone to give the oxalate (0.254 g) of the title compound as orange crystals.

m.p. (oxalate): 182°C.

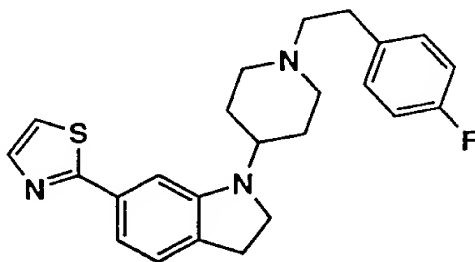
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.92(4H, m), 2.95(2H, t, J=8.4Hz), 2.99(2H, m), 3.04(2H, m), 3.17(2H, m), 3.40(2H, t, J=8.4Hz), 3.56(2H, br-d), 3.86(1H, m), 7.17(4H, m), 7.32(4H, m), 7.85(2H, m), 8.62(1H, d, J=4.4Hz).

FAB-Mass: 402(MH+).

Example 172: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-thiazolyl)indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-bromoindoline (0.56 g) and 2-tributylstannylthiazole (2.778 g) synthesized in accordance with the method described in Synthesis, 757 (1986). were treated as in Production Example 13-2 to give the title compound (0.017 g) as pale yellow crystals (yield: 3.0%).

Next, oxalic acid (2 mg) was added to the above product to give an oxalate followed by recrystallization from acetone to give the oxalate of the title compound as yellow crystals.

m.p. (oxalate): 170°C.

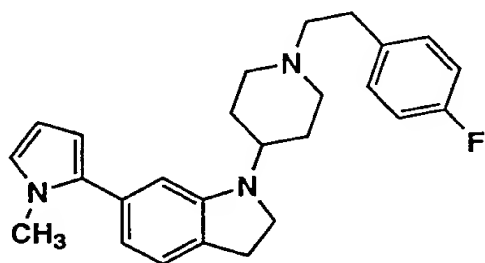
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.90(4H, m), 2.95(2H, t, J=8.4Hz), 2.98(2H, m), 3.04(2H, m), 3.16(2H, m), 3.42(2H, t, J=8.4Hz), 3.56(2H, m), 3.85(1H, m), 7.06(1H, s), 7.13(2H, m), 7.33(2H, m), 7.71(1H, d, J=3.2Hz), 7.86(1H, d, J=3.2Hz).

FAB-Mass: 408(MH⁺).

Example 173: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(1-methylpyrrol-2-yl)indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-bromoindoline (0.1 g) and 1-methyl-2-tributylstannylpyrrole (0.37 g) synthesized in accordance with the method described in Tetrahedron Lett., 4407 (1986). were treated as in Production Example 13-2 to give the title compound (0.016 g) as a yellow oil (yield: 15.8%).

Next, oxalic acid (2 mg) was added to the above product to give an oxalate followed by recrystallization from acetone to give the oxalate of the title compound as yellow crystals.

m.p. (oxalate): 118°C.

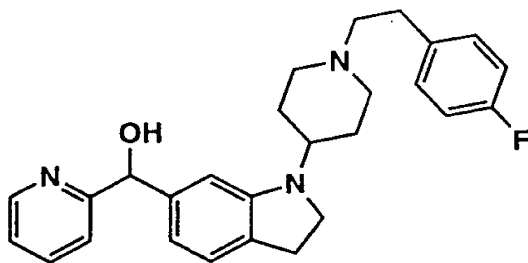
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.83(4H, m), 2.79(2H, m), 2.90(2H, t, J=8.4Hz), 2.92(2H, m), 3.02(2H, m), 3.37(2H, t, J=8.4Hz), 3.41(2H, m), 3.60(3H, s), 3.68(1H, m), 6.01(1H, dd, J=2.4, 3.6Hz), 6.05(1H, dd, J=2.0, 3.6Hz), 6.51(1H, d, J=1.2Hz), 6.58(1H, dd, J=1.2, 7.6Hz), 6.78(1H, dd, J=2.0, 2.4Hz), 7.04(1H, d, J=7.6Hz), 7.15(2H, m), 7.31(2H, m).

ESI-Mass: 404.2(MH⁺).

Example 174: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[1-hydroxy-1-(2-pyridyl)methyl]indoline



2-Bromopyridine (0.16 ml), 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-formylindoline (0.5 g) and diethyl ether employed as the solvent were treated as in Example 93 to give the title compound (0.344 g) as a yellow oil (yield: 56.1%).

To a 50 mg portion of the above product was added oxalic acid (10 mg) to give the oxalate of the title compound.

m.p. (oxalate): 105°C.

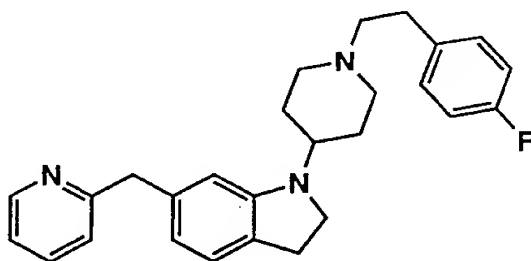
Free

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.72-1.81(4H, m), 2.08-2.19(2H, m), 2.57-5.61(2H, m), 2.78-2.82(2H, m), 2.91(1H, t, J=8.4Hz), 3.10(2H, br-t), 3.38(2H, t, J=8.4Hz), 3.40(1H, m), 5.21(1H, d, J=4.0Hz), 5.66(1H, d, J=4.0Hz), 6.43(1H, d, J=1.2Hz), 6.56(1H, dd, J=1.2, 7.2Hz), 6.95-6.99(3H, m), 7.13-7.26(4H, m), 7.60(1H, ddd, J=1.6, 7.2, 8.8Hz), 8.54(1H, ddd, J=0.8, 1.6, 4.0Hz).

ESI-Mass: 432.2(MH⁺).

Example 175: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[1-(2-pyridyl)methyl]indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-[1-hydroxy-1-(2-pyridyl)methyl]indoline (0.321 g) was dissolved in ethanol (86.4 ml) followed by the addition of 1 N hydrochloric acid (3.7 ml) and palladium carbon. Then the resultant mixture was catalytically reduced under atmospheric pressure for 3 hr. After filtering off the catalyst, the filtrate was concentrated under reduced pressure. To the residue were added a saturated aqueous solution of sodium bicarbonate and ethyl acetate and

the layers were separated. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Then the residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate-methanol system) to give the title compound (0.076 g) as a yellow oil (yield: 24.6%).

Then oxalic acid (16.5 mg) was added to the above product to give the oxalate of the title compound as a yellow hygroscopic amorphous solid.

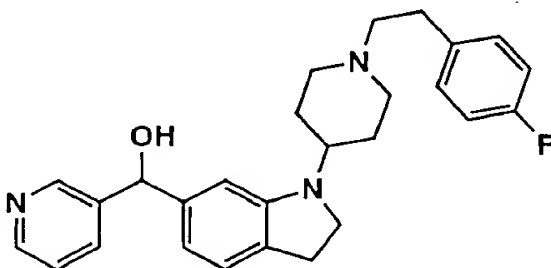
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.77(4H, m), 2.67(2H, m), 2.81(2H, t, J=8.2Hz), 2.87-2.93(4H, m), 3.30(2H, t, J=8.2Hz), 3.36(2H, br-d), 3.95(1H, m), 4.17(2H, s), 6.42-6.44(2H, m), 6.91(1H, d, J=7.5Hz), 7.12-7.21(4H, m), 7.29-7.32(2H, m), 7.67(1H, ddd, J=1.8, 6.0, 6.0Hz), 8.46(1H, dd, J=0.8, 4.8Hz).

FAB-Mass: 416(MH+).

Example 176: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[1-hydroxy-1-(3-pyridyl)methyl]indoline



3-Bromopyridine (0.44 ml), 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-formylindoline (0.4 g) and diethyl ether employed as the solvent were treated as in Example 93 to give the title compound (0.337 g) as a yellow oil (yield: 68.8%).

Then oxalic acid was added to the above product to give the oxalate of the title compound as an amorphous solid.

m.p. (oxalate): 110 - 113°C.

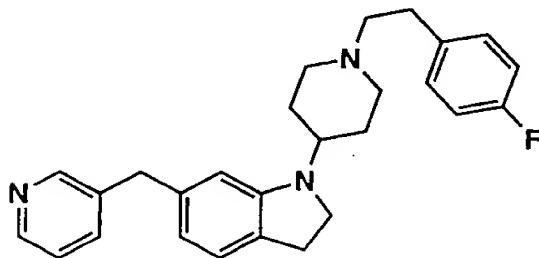
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.88(4H, m), 2.83(2H, t, J=8.5Hz), 3.01(4H, m), 3.19(2H, m), 3.30(2H, t, J=8.5Hz), 3.57(2H, m), 3.71(1H, m), 5.65(1H, s), 6.56(1H, d, J=7.6Hz), 6.59(1H, s), 6.95(1H, d, J=7.6Hz), 7.18(2H, m), 7.32(3H, m), 7.70(1H, ddd, J=1.6, 2.0, 6.0Hz), 8.40(1H, dd, J=1.6, 5.2Hz), 8.57(1H, d, J=2.0Hz).

ESI-Mass: 432.2(MH⁺).

Example 177: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[1-(3-pyridyl)methyl]indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-[1-hydroxy-1-(3-pyridyl)methyl]indoline (0.1 g) was treated as in Example

175 to give the title compound (0.018 g) as a colorless oil (yield: 18.7%).

Free

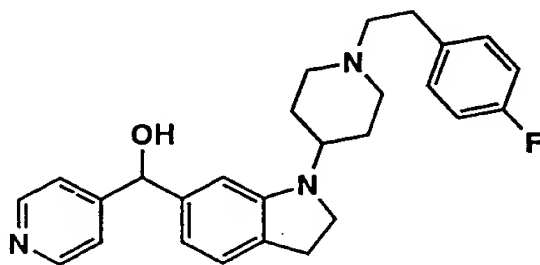
¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.79(4H, m), 2.14(2H, m), 2.61(2H, m), 2.81(2H, m), 2.91(2H, t, J=8.4Hz), 3.13(2H, br-d), 3.25(1H, m), 3.40(2H, t, J=8.4Hz), 3.88(2H, s), 6.19(1H, d, J=1.2Hz), 6.41(1H, dd, J=1.2, 7.4Hz), 6.97(3H, m), 7.17(3H, m), 7.47(1H, m), 8.44(1H, dd, J=1.2, 4.8Hz), 8.51(1H, d, J=1.2Hz).

ESI-Mass: 416.2(MH⁺).

Next, oxalic acid (5 mg) was added to the above product to give the oxalate of the title compound as an amorphous solid.

Example 178: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(1-hydroxy-4-pyridylmethyl)indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-bromoindoline (700 mg), a 2.5 M solution (1.0 ml) of n-butyllithium in hexane and 4-pyridinecarbaldehyde (280 mg) were treated as in Example 130 to give the oxalate (130 mg) of the title compound as a brown hygroscopic amorphous substance

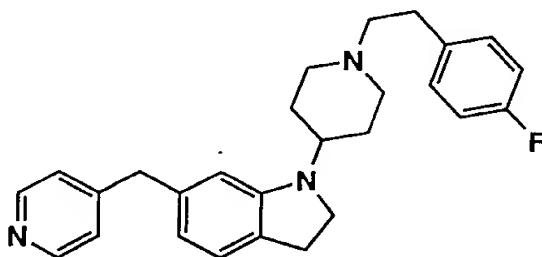
(yield: 15%).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.75-1.93(4H, m), 2.83(2H, t, J=8Hz), 2.91-3.02(4H, m), 3.11-3.19(2H, m), 3.30(2H, t, J=8Hz), 3.48-3.57(2H, m), 3.61-3.71(1H, m), 5.57(1H, s), 6.55-6.57(2H, m), 6.94(1H, d, J=8Hz), 7.15-7.20(2H, m), 7.31-7.36(4H, m), 8.45-8.47(2H, m).

FAB-Mass: 432(MH⁺).

Example 179: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(4-pyridylmethyl)indoline



A mixture of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1'-hydroxy-4-pyridylmethyl)indoline (350 mg), 10% palladium carbon (200 mg), 5 N hydrochloric acid (0.8 ml) and ethanol (20 ml) was catalytically reduced under hydrogen atmosphere of 3 atm. After 5 hr, the catalyst was filtered off and the filtrate was concentrated under reduced pressure. Then the residue was diluted with a saturated aqueous solution of sodium bicarbonate and ethyl acetate and the layers were separated. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. Then the residue was

purified by NH-silica gel column chromatography (hexane/ethyl acetate system) followed by conversion into an oxalate in a conventional manner to give the oxalate (190 mg) of the title compound as a white powder (yield: 46%).

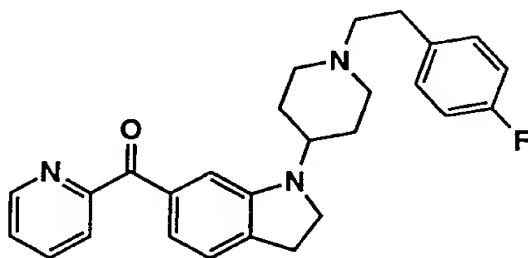
m.p. (oxalate): 195 - 197°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.79-1.94(4H, m), 2.84(2H, t, J=8Hz), 2.92-2.90(4H, m), 3.11-3.19(2H, m), 3.32(2H, t, J=8Hz), 3.48-3.56(2H, m), 3.59-3.69(1H, m), 3.83(2H, s), 6.41-6.43(2H, m), 6.94(1H, d, J=8Hz), 7.15-7.22(4H, m), 7.30-7.34(2H, m), 8.42-8.44(2H, m).

FAB-Mass: 416(MH⁺).

Example 180: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(2-pyridylcarbonyl)indoline

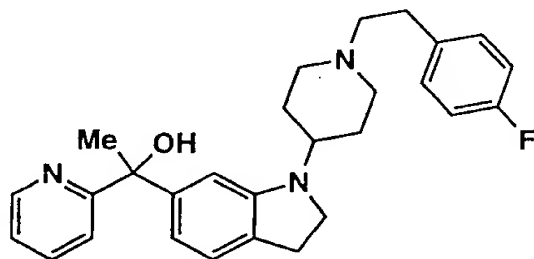


1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-[1-hydroxy-1-(2-pyridyl)methyl]indoline (0.895 g) was treated in accordance with the method described in J. Org. Chem., 2899 (1993). to give the title compound (0.357 g) as a yellow oil (yield: 40.1%).

¹H-NMR (400 MHz, CDCl₃):

δ (ppm) 1.81(4H, m), 2.18(2H, m), 2.60(2H, m), 2.80(2H, m), 3.01(2H, t, J=8.4Hz), 3.11(2H, m), 3.47(2H, t, J=8.4Hz), 3.51(1H, m), 6.97(2H, m), 7.02(1H, d, J=0.6Hz), 7.09(1H, d, J=7.2Hz), 7.17(3H, m), 7.45(1H, ddd, J=1.4, 5.0, 7.6Hz), 7.87(1H, ddd, J=1.8, 7.6, 7.6Hz), 7.93(1H, ddd, J=0.8, 1.4, 7.6Hz), 8.71(1H, ddd, J=0.8, 1.8, 5.0Hz).

Example 181: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[1-hydroxy-1-(2-pyridyl)ethyl]indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-(2-pyridylcarbonyl)indoline (0.074 g) was dissolved in tetrahydrofuran (1.0 ml). To the resultant solution was added at -78°C a 3.0 M solution of methylmagnesium bromide in diethyl ether and the resultant mixture was stirred for 1 hr. Next, water and ethyl acetate were added thereto and the layers were separated. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate-methanol system) to give the title compound (0.029 g) as a yellow oil (yield: 37.8%).

Next, oxalic acid (6 mg) was added to the above product to give the oxalate of the title compound as a yellow amorphous solid.

m.p. (oxalate): 98 - 108°C.

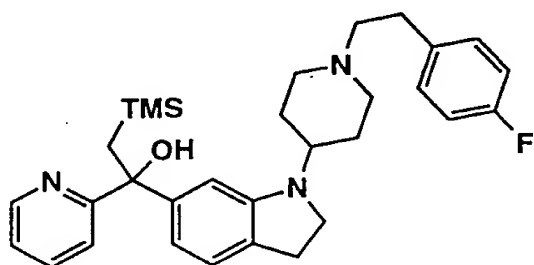
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.84(4H, m), 2.80(2H, t, J=8.4Hz), 2.99(2H, m), 3.11(2H, m), 3.24(2H, m), 3.28(2H, t, J=8.4Hz), 3.59(2H, m), 3.70(1H, m), 6.61(1H, d, J=7.4Hz), 6.69(1H, s), 6.88(1H, d, J=7.4Hz), 7.19(3H, m), 7.36(2H, m), 7.58(1H, m), 7.71(1H, m), 8.46(1H, m).

ESI-Mass: 446.3(MH⁺).

Example 182-1: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[1-hydroxy-1-(2-pyridyl)-2-trimethylsilylethyl]indoline



(wherein TMS means trimethylsilyl.)

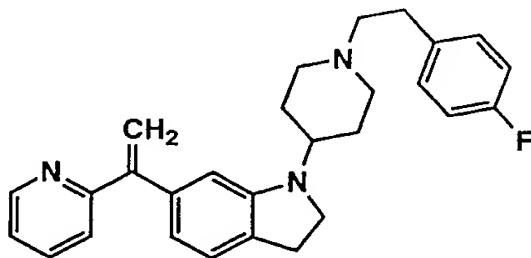
1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-[1-hydroxy-1-(2-pyridyl)ethyl]indoline (0.357 g) was treated in accordance with the method described in Synthesis, 384 (1984).

to give the title compound (0.250 g) as a yellow oil (yield: 58.3%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) -0.75(9H, s), 1.75(4H, m), 2.13(2H, m), 2.58(2H, m), 2.78(2H, m), 2.87(3H, t, J=8.4Hz), 3.09(2H, m), 3.36(2H, t, J=8.4Hz), 3.43(1H, m), 5.99(2H, s), 6.64(1H, d, J=1.2Hz), 6.76(1H, dd, J=1.2, 7.6Hz), 6.94(1H, d, J=7.6Hz), 6.97(2H, m), 7.11(1H, ddd, J=0.8, 4.8, 7.6Hz), 7.15(2H, m), 7.39(1H, ddd, J=0.8, 0.8, 8.0Hz), 7.59(1H, ddd, J=1.6, 7.6, 8.0Hz), 8.45(1H, ddd, J=0.8, 1.6, 4.8Hz).

Example 182-2: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[1-(2-pyridyl)vinyl]indoline



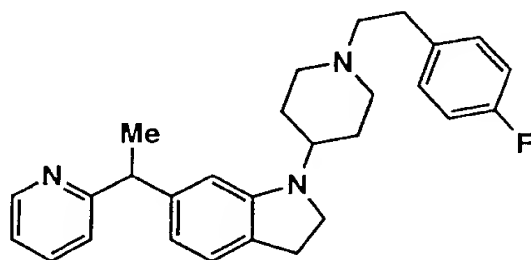
1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-[1-hydroxy-1-(2-pyridyl)-2-trimethylsilylethyl]indoline (0.250 g) was treated in accordance with the method described in J. Am. Chem. Soc., 1464 (1975). to give the title compound (0.138 g) as a yellow oil (yield: 66.6%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.80(4H, m), 2.07(2H, m), 2.56(2H, m), 2.77(2H, m), 2.97(2H, t, J=8.4Hz), 3.08(2H, br-d), 3.36(1H, m), 3.43(2H, t,

J=8.4Hz), 5.40(1H, d, J=1.8Hz), 5.98(1H, d, J=1.8Hz), 6.37(1H, d, J=1.2Hz), 6.57(1H, dd, J=1.2, 7.6Hz), 6.96(2H, m), 7.03(1H, d, J=7.6Hz), 7.14(2H, m), 7.20(1H, ddd, 0.6, 5.0, 7.6Hz), 7.27(1H, ddd, 0.4, 0.6, 7.2Hz), 7.60(1H, ddd, 2.0, 7.2, 7.6Hz), 8.64(1H, ddd, 0.4, 2.0, 5.0Hz).

Example 182-3: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[1-(2-pyridyl)ethyl]indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-[1-(2-pyridyl)vinyl]indoline (0.138 g) was treated as in Production Example 59-2 to give the title compound (0.110 g) as a yellow oil (yield: 79.3%).

Next, oxalic acid (23 mg) was added to the above product to give the oxalate of the title compound as an amorphous solid. m.p. (oxalate): 95 - 102°C.

Oxalate

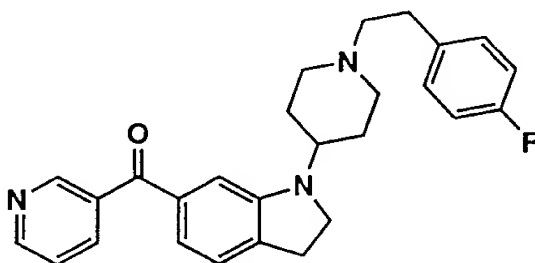
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.58(3H, d, J=7.2Hz), 1.83(4H, m), 2.81(2H, t, J=8.0Hz), 2.96(2H, m), 3.16(2H, m), 3.29(2H, t, J=8.0Hz), 3.53(2H, m), 3.67(1H, m), 4.14(1H, q, J=7.2Hz), 6.48(2H, m),

6.91(1H, d, J=7.6Hz), 7.18(4H, m), 7.33(2H, m), 7.66(1H, ddd, J=1.6, 7.6, 7.6Hz), 8.48(1H, m).

ESI-Mass: 430.3(MH+).

Example 183: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(3-pyridylcarbonyl)indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-[1-hydroxy-1-(3-pyridyl)methyl]indoline (0.121 g) was treated in accordance with the method described in J. Org. Chem., 2899 (1993). to give the title compound (0.009 g) as a yellow oil (yield: 7.5%).

Free

¹H-NMR (400 MHz, CDCl₃):

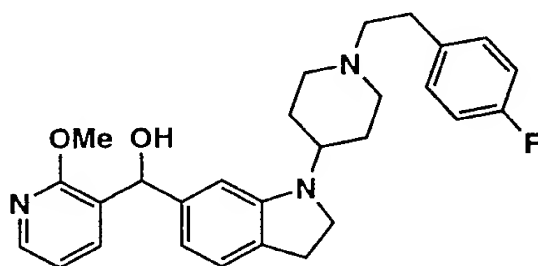
δ(ppm) 1.84(4H, m), 2.17(2H, m), 2.61(2H, m), 2.80(2H, m), 3.04(2H, t, J=8.4Hz), 3.14(2H, m), 3.49(1H, m), 3.51(2H, t, J=8.4Hz), 6.87(1H, t, J=1.6Hz), 6.93(1H, dd, J=1.6, 7.2Hz), 6.98(2H, m), 7.10(1H, d, J=7.2Hz), 7.16(2H, m), 7.43(1H, ddd, J=0.8, 4.8, 7.2Hz), 8.10(1H, ddd, J=1.6, 2.0, 7.2Hz), 8.78(1H, dd, J=0.8, 4.8Hz), 8.97(1H, dd, J=0.8, 2.0Hz).

ESI-Mass: 430.2(MH+).

Next, oxalic acid (2 mg) was added to the above product to give the oxalate of the title compound.

m.p. (oxalate): 115°C.

Example 184: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[1-hydroxy-1-(2-methoxypyridin-3-yl)-methyllindoline



2-Methoxypyridine (0.3 ml) and 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-formylindoline (0.5 g) were treated in accordance with the method described in J. Org. Chem., 1367 (1988). to give the title compound (0.493 g) as a pale yellow oil (yield: 75.2%).

Next, oxalic acid was added thereto to give the oxalate of the title compound as an amorphous solid.

m.p. (oxalate): 101°C.

Oxalate

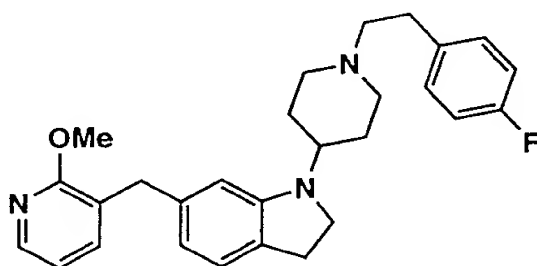
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.82(4H, m), 2.81(2H, t, J=8.4Hz), 2.96(4H, m), 3.14(2H, m), 3.31(2H, t, J=8.4Hz), 3.53(2H, m), 3.67(1H, m), 3.84(3H, s), 5.75(1H, s), 6.49(1H, dd, J=0.8, 7.4Hz), 6.55(1H,

d, J=0.8Hz), 6.91(1H, d, J=7.4Hz), 6.98(1H, dd, J=5.2, 7.6Hz), 7.16(2H, m), 7.33(2H, m), 7.79(1H, dd, J=2.0, 7.6Hz), 8.02(1H, dd, J=2.0, 5.2Hz).

ESI-Mass: 462.3(MH+).

Example 185: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[1-(2-methoxypyridin-3-yl)methyl]indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-[1-hydroxy-1-(2-methoxypyridin-3-yl)methyl]indoline (0.418 g) was treated as in Example 175 to give the title compound (0.040 g) as a pale yellow oil (yield: 9.9%).

Next, oxalic acid (8 mg) was added thereto to give the oxalate of the title compound as an amorphous solid.

m.p. (oxalate): 182°C.

Oxalate

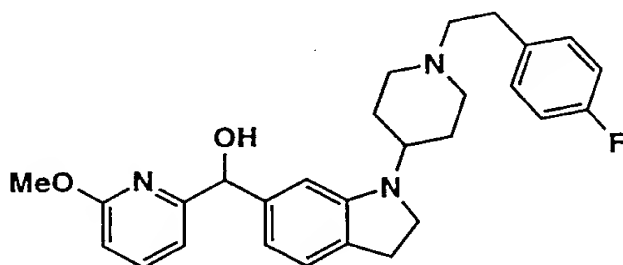
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.85(4H, m), 2.83(2H, t, J=8.4Hz), 2.96(4H, m), 3.17(2H, m), 3.31(2H, t, J=8.4Hz), 3.54(2H, m), 3.65(1H, m), 3.75(2H, s), 3.87(3H, s), 6.39(1H, d, J=7.6Hz), 6.41(1H, s), 6.90(1H, dd, J=5.2, 7.6Hz), 6.92(1H, d, J=7.6Hz), 7.18(2H, m),

7.33(2H, m), 7.39(1H, dd, J=2.0, 7.6Hz), 8.01(1H, dd, J=2.0, 5.2Hz).

ESI-Mass: 446.3(MH+).

Example 186: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[1-hydroxy-1-(2-methoxypyridin-6-yl)-methyllindoline



Tetramethylethylenediamine (0.26 ml) was added to 6-bromo-2-methoxypyridine (0.32 g) synthesized in accordance with the method described in Tetrahedron, 1373 (1985). and 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-formylindoline (0.4 g) and diethyl ether was employed as the solvent. The resultant mixture was treated as in Example 93 to give the title compound (0.401 g) as colorless crystals (yield: 76.5%).

Next, oxalic acid was added thereto to give the oxalate of the title compound as an amorphous solid.

m.p. (oxalate): 95°C.

Oxalate

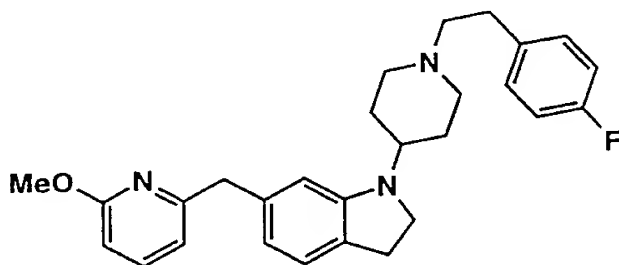
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.84(2H, m), 2.16(2H, m), 2.82(2H, t, J=8.4Hz),

2.99(4H, m), 3.16(2H, t), 3.30(2H, t, J=8.4Hz), 3.54(2H, m), 3.68(1H, m), 3.81(3H, s), 5.48(1H, s), 6.52(3H, m), 6.92(1H, d, J=7.9Hz), 7.09(1H, d, J=7.1Hz), 7.16(3H, m), 7.34(2H, m), 7.65(1H, d, J=7.6Hz).

FAB-Mass: 462(MH+).

Example 187: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[1-(2-methoxypyridin-6-yl)methyl]indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-[1-hydroxy-1-(2-methoxypyridin-6-yl)methyl]indoline (0.363 g) was treated as in Example 175 to give the title compound (0.127 g) as a pale yellow oil (yield: 39.2%).

Next, oxalic acid (26 mg) was added thereto to give the oxalate of the title compound as an amorphous solid.

m.p. (oxalate): 139°C.

Oxalate

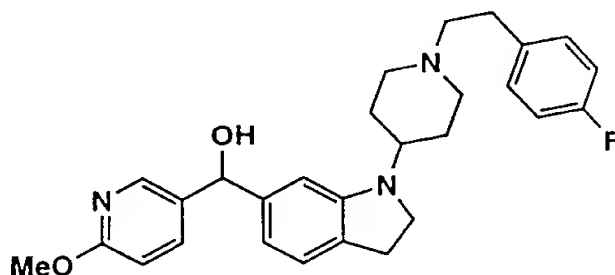
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.83(4H, m), 2.84(2H, t, J=8.4Hz), 2.87(2H, m), 2.93(2H, m), 3.06(2H, m), 3.31(2H, t, J=8.4Hz), 3.45(2H, m), 3.64(1H, m), 3.83(3H, s), 3.85(2H, s), 6.47(2H, m), 6.60(1H, d, J=8.2Hz), 6.75(1H, d, J=7.3Hz), 6.93(1H, d, J=8.0Hz),

7.16(2H, m), 7.32(2H, m), 7.57(1H, dd, J=7.3, 8.2Hz).

FAB-Mass: 446(MH+).

Example 188: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[1-hydroxy-1-(2-methoxypyridin-5-yl)-methyllindoline



A mixture of 5-bromo-2-methoxypyridine (0.32 g) synthesized in accordance with the method described in Tetrahedron, 1373 (1985). and 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-formylindoline (0.4 g) and diethyl ether employed as a solvent was treated as in Example 93 to give the title compound (0.461 g) as a pale yellow oil (yield: 88.0%).

Free

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.79(4H, m), 2.13(2H, m), 2.48(1H, br-d), 2.60(2H, m), 2.80(2H, m), 2.92(2H, t, J=8.4Hz), 3.11(2H, br-d), 3.38(1H, m), 3.41(2H, t, J=8.4Hz), 3.91(1H, ddd, J=0.4, 0.4, 2.8 Hz), 5.72(1H, d, J=2.4Hz), 6.42(1H, d, J=0.8Hz), 6.55(1H, dd, J=0.8Hz), 6.68(1H, dd, J=0.4, 8.8Hz), 6.97(3H, m), 7.15(2H, m), 7.56(1H, ddd, J=0.4, 2.4, 8.8Hz), 8.17(1H, ddd, J=0.4, 0.4,

2.4Hz).

ESI-Mass: 462.2(MH+).

Next, oxalic acid or hydrochloric acid was added thereto to give the oxalate or the hydrochloride as a hygroscopic amorphous solid of the title compound.

Oxalate

M.p. (oxalate): 108°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.76(4H, m), 2.63(4H, m), 2.86(2H, t, J=8.2Hz), 3.89(4H, m), 3.31(2H, t, J=8.2Hz), 3.33(2H, m), 3.55(1H, m), 3.80(3H, s), 5.58(1H, s), 6.54(1H, s), 6.72(1H, d, J=8.6Hz), 6.92(1H, d, J=7.6Hz), 7.14(2H, t, J=8.2Hz), 7.30(2H, dd, J=5.6, 8.2Hz), 7.57(1H, dd, J=2.2, 8.6Hz), 8.13(1H, d, J=2.2Hz).

Oxalate

FAB-Mass: 462(MH+).

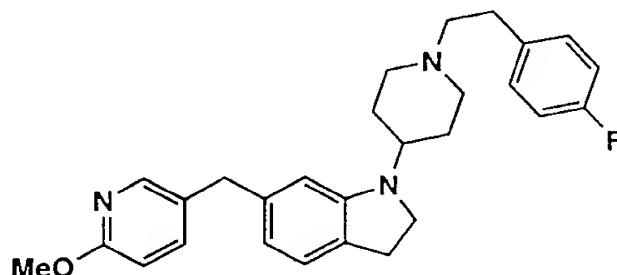
Hydrochloride

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.86(2H, m), 2.10(2H, m), 2.86(2H, t, J=8.4Hz), 3.11(4H, m), 3.24(2H, m), 3.34(2H, t, J=8.4Hz), 3.64(2H, m), 3.75(1H, m), 3.82(3H, s), 5.61(1H, s), 6.55(1H, s), 6.58(1H, d, J=7.6Hz), 6.67(1H, br-s), 6.78(1H, d, J=8.4Hz), 6.97(1H, d, J=7.6Hz), 7.19(2H, m), 7.34(2H, m), 7.63(1H, dd, J=2.4, 8.4Hz), 8.16(1H, d, J=2.4Hz).

FAB-Mass: 462(MH+).

Example 189: Synthesis of 1-[1-(4-fluorophenethyl)-
piperidin-4-yl]-6-[1-(2-methoxypyridin-5-yl)methyl]indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-[1-hydroxy-
1-(2-methoxypyridin-5-yl)methyl]indoline (0.335 g) was
treated as in Example 175 to give the title compound (0.046 g)
as a pale yellow oil (yield: 14.2%).

Next, oxalic acid (10 mg) was added thereto to give the
oxalate of the title compound.

m.p. (oxalate): 166°C.

Oxalate

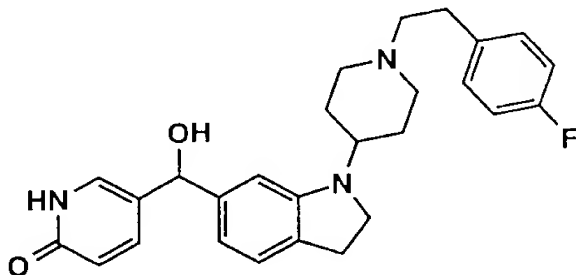
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.57(4H, m), 1.85(2H, m), 2.30(2H, m), 2.80(2H, m),
2.93(2H, t, J=8.4Hz), 3.21(2H, m), 3.42(2H, t, J=8.4Hz),
3.46(1H, m), 4.0(3H, s), 4.89(1H, d, J=4.2Hz), 5.59(1H, d,
J=4.2Hz), 6.45(1H, d, J=1.1Hz), 6.60(1H, d, J=7.3Hz), 6.62(1H,
d, J=8.2Hz), 6.71(1H, d, J=7.3Hz), 6.99(2H, m), 7.00(1H, d,
J=7.3Hz), 7.18(2H, m), 7.50(1H, dd, J=7.3, 8.2Hz).

FAB-Mass: 446(MH+).

Example 190: Synthesis of 1-[1-(4-fluorophenethyl)-

piperidin-4-yl]-6-[1-hydroxy-1-(2-pyridon-5-yl)methyl]-
indoline



The hydrochloride (0.101 g) of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[1-hydroxy-1-(2-methoxypyridin-5-yl)methyl]indoline which had been prepared about one month before was allowed to stand at room temperature for 2 months. Then, it was dissolved in ethyl acetate and mixed with a saturated aqueous solution of sodium bicarbonate and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Next, the residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (0.033 g) as pale yellow crystals.

m.p. (free): 202°C.

Free

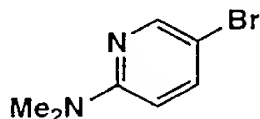
¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.82(4H, m), 2.31(2H, m), 2.68(2H, m), 2.86(2H, m), 2.92(2H, t, J=8.4Hz), 3.19(2H, m), 3.38(1H, m), 3.42(2H, t, J=8.4Hz), 5.53(1H, s), 6.38(1H, br-s), 6.47(1H, d, J=932Hz),

6.54(1H, dd, J=0.8, 7.2Hz), 6.95-7.01(3H, m), 7.14-7.17(2H, m), 7.32(1H, d, J=2.4Hz), 7.44(1H, dd, J=2.4, 9.2Hz).

FAB-Mass: 448(MH+).

Example 191-1: Synthesis of 5-bromo-2-dimethylaminopyridine

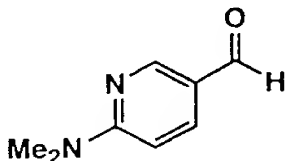


2-Dimethylaminopyridine (1.0 ml) was dissolved in chloroform (60 ml). After adding tributylammonium bromide (3.88 g) thereto, the resultant mixture was stirred for 7 min. Then the reaction solution was washed with an aqueous solution of sodium thiosulfate and water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate-methanol system) to give the title compound (1.097 g) as yellow crystals (yield: 72.0%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 3.05(6H, s), 6.40(1H, dd, J=0.8, 8.8Hz), 7.48(1H, dd, J=2.8, 8.8Hz), 8.16(1H, dd, J=0.8, 2.8Hz).

Example 191-2: Synthesis of 2-dimethylamino-5-formylpyridine



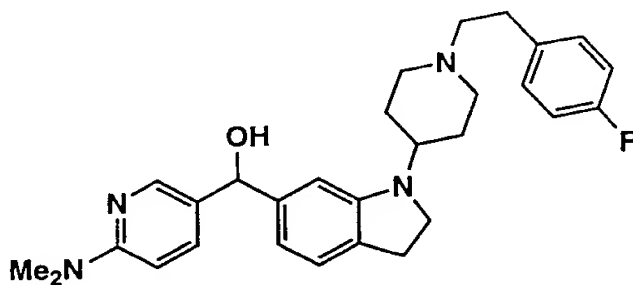
Tetramethylethylenediamine (8.0 ml) was added to the

mixture of 5-bromo-2-dimethylaminopyridine (5.0 g), N,N-dimethylformamide (6.1 ml) and diethyl ether employed as the solvent. The resultant mixture was treated in as in Example 93 to give the title compound (3.273 g) as pale yellow crystals (yield: 89.6%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 3.21(6H, s), 6.56(1H, dd, J=0.4, 9.2Hz), 7.91(1H, dd, J=2.4, 9.2Hz), 8.55(1H, dd, J=0.4, 2.4Hz), 9.77(1H, s).

Example 191-3: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[1-hydroxy-1-(2-dimethylaminopyridin-5-yl)methyl]indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-bromoindoline (0.5 g) and 2-dimethylamino-5-formylpyridine (0.345 g) were treated as in Example 130 to give the title compound (0.376 g) as a colorless oil (yield: 65.3%).

Next, hydrochloric acid was added thereto to give the hydrochloride of the title compound as an amorphous solid.

m.p. (hydrochloride): 185 - 196°C.

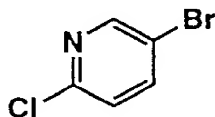
Hydrochloride

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.86(2H, m), 2.08-2.18(2H, m), 2.86(2H, t, J=8.4Hz), 3.07-3.15(4H, m), 3.21(6H, s), 3.71(2H, m), 3.34(2H, t, J=8.4Hz), 3.64(2H, br-d), 3.73(1H, m), 5.63(1H, s), 6.56(1H, d, J=7.4Hz), 6.69(1H, s), 6.98(1H, t, J=7.4Hz), 7.18(3H, m), 7.34(2H, m), 7.85(1H, dd, J=2.0, 9.6Hz), 7.90(1H, d, J=2.0Hz).

ESI-Mass: 475.2(MH⁺).

Example 192-1: Synthesis of 5-bromo-2-chloropyridine

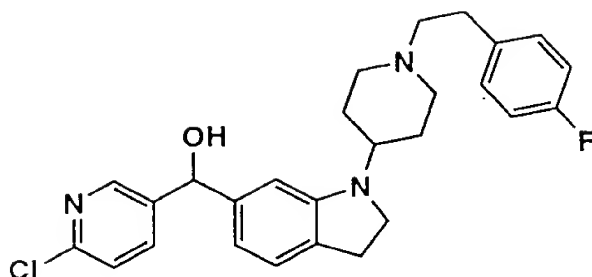


5-Bromo-2-methoxypyridine (1.88 g) was treated in accordance with the method described in Synth. Commun., 2971 (1990). to give the title compound (0.046 g) as a pale yellow oil (yield: 14.2%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 7.24(1H, dd, J=0.4, 8.1Hz), 7.77(1H, dd, J=2.4, 8.1Hz), 8.47(1H, dd, J=0.4, 2.4Hz).

Example 192-2: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[1-hydroxy-1-(2-chloropyridin-5-yl)-methyllindoline



5-Bromo-2-chloropyridine (0.151 g) and 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-formylindoline (0.2 g) were treated as in Example 93 to give the title compound (0.130 g) as a colorless oil (yield: 49.7%).

Next, hydrochloric acid was added thereto to give the hydrochloride of the title compound as an amorphous solid. m.p. (hydrochloride): 136°C.

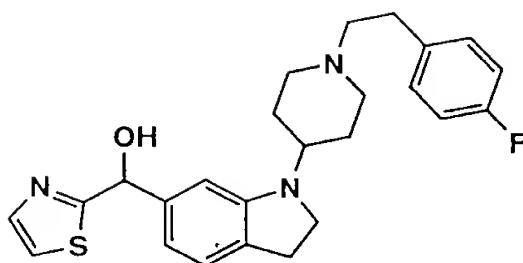
Hydrochloride

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.84(2H, m), 2.12(2H, m), 2.84(2H, t, J=8.4Hz), 3.04-3.17(4H, m), 3.16(2H, t, J=8.4Hz), 3.65(2H, br-d), 3.74(1H, m), 5.68(1H, s), 6.58(1H, d, J=7.6Hz), 6.64(1H, s), 6.97(1H, d, J=7.6Hz), 7.19(2H, m), 7.34(2H, m), 7.43(1H, d, J=8.4Hz), 7.76(1H, dd, J=2.4, 8.4Hz), 8.42(1H, d, J=2.4Hz).

ESI-Mass: 466.1(MH⁺).

Example 193: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[1-(2-thiazolyl)-1-hydroxymethyl]indoline



Thiazole (0.12 ml) was dissolved in tetrahydrofuran (5 ml). In a nitrogen atmosphere at -78°C , a 1.66 M solution (1.0 ml) of n-butyllithium in n-hexane was added dropwise into the solution obtained above and the resultant mixture was stirred under the same conditions for 10 min. Next, 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-formylindoline (0.5 g) dissolved in tetrahydrofuran (7 ml) was added thereto and the resultant mixture was stirred at -78°C for 3 hr. To the reaction solution were successively added a saturated aqueous solution of ammonium chloride and ethyl acetate (200 ml) and the layers were separated. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate/methanol system) to give the title compound (0.134 g) as a pale yellow oil (yield: 32.6%).

Next, oxalic acid (3 mg) was added to 40 mg of the above product to give the oxalate of the title compound as a colorless amorphous solid.

m.p. (oxalate): 118°C.

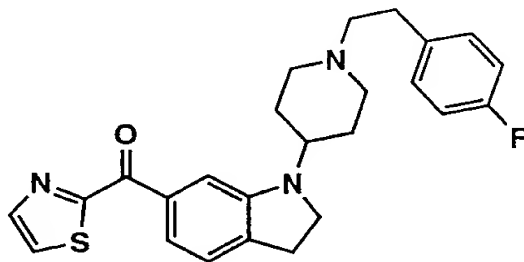
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.78(4H, m), 2.84(2H, t, J=8.6Hz), 2.89(4H, m), 2.95(2H, m), 3.32(2H, t, J=8.6Hz), 3.37(2H, m), 3.58(1H, m), 4.81(1H, s), 5.56(1H, s), 6.00(1H, d, J=7.2Hz), 6.95(1H, d, J=7.2Hz), 7.15(2H, m), 7.31(2H, m), 7.59(1H, d, J=3.0Hz), 7.66(1H, d, J=3.0Hz).

ESI-Mass: 438.2(MH⁺).

Example 194: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(2-thiazolylcarbonyl)indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-[1-(2-thiazolyl)-1-hydroxymethyl]indoline (0.1 g) was treated in accordance with the method described in J. Org. Chem., 2480 (1978). to give the title compound (0.022 g) as a yellow oil (yield: 22.1%).

Next, oxalic acid (5 mg) was added thereto to give the oxalate of the title compound as a colorless amorphous solid.
m.p. (oxalate): 132°C.

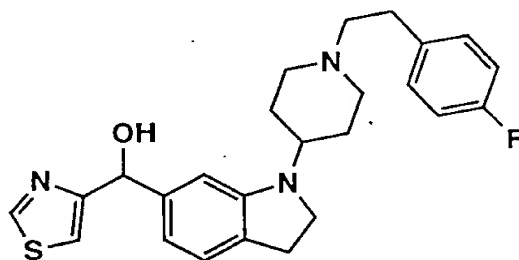
Free

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.51(4H, m), 1.82(2H, m), 2.62(2H, m), 2.80(2H, m), 2.97(2H, t, J=8.4Hz), 3.14(2H, m), 3.43(2H, t, J=8.4Hz), 3.49(1H, m), 6.20(2H, m), 7.11(3H, m), 7.17(1H, br-s), 7.61(1H, d, J=3.2Hz), 7.89(1H, d, J=7.6Hz), 7.99(1H, d, J=3.2Hz).

FAB-Mass: 436(MH⁺).

Example 195: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[1-(4-thiazolyl)-1-hydroxymethyl]indoline



4-Bromo-2-trimethylsilylthiazole (0.2 g) synthesized in accordance with the method described in J. Org. Chem., 1749 (1988). and 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-formylindoline (0.2 g) were treated as in Example 193 to give the title compound (0.039 g) as a pale yellow oil (yield: 15.7%).

Next, oxalic acid (4 mg) was added thereto to give the oxalate of the title compound as an amorphous solid.

m.p. (oxalate): 115°C.

Oxalate

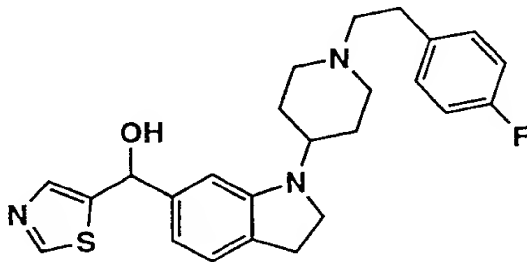
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.78(4H, m), 2.74(2H, m), 2.83(2H, t, J=8.4Hz),

2.89(2H, m), 2.97(2H, m), 3.31(2H, t, J=8.4Hz), 3.38(2H, m), 3.57(1H, m), 5.72(1H, s), 6.55(2H, m), 6.92(1H, d, J=7.2Hz), 7.15(2H, m), 7.31(2H, m), 7.44(1H, dd, J=0.4, 2.0Hz), 8.96(1H, d, J=2.0Hz).

FAB-Mass: 438(MH+).

Example 196: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[1-(5-thiazolyl)-1-hydroxymethyl]indoline



2-Trimethylsilylthiazole (0.134 g) and 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-formylindoline (0.2 g) were treated as in Example 193 to give the title compound (0.145 g) as a pale yellow oil (yield: 58.4%).

Next, oxalic acid (15 mg) was added thereto to give the oxalate of the title compound as an amorphous solid.

m.p. (oxalate): 112°C.

Oxalate

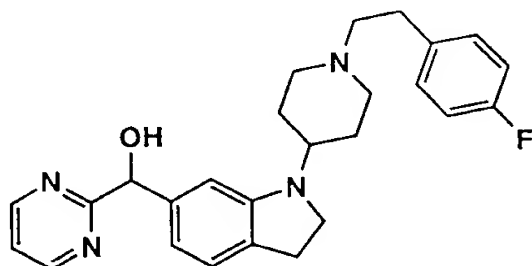
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.80(4H, m), 2.86(2H, t, J=8.4Hz), 2.91(4H, m), 3.04(2H, m), 3.33(2H, t, J=8.4Hz), 3.46(2H, m), 3.62(1H, m), 5.90(1H, s), 6.58(2H, m), 6.97(1H, d, J=7.2Hz), 7.16(2H, m),

7.31(2H, m), 7.66(1H, s), 8.93(1H, s).

FAB-Mass: 438(MH+).

Example 197: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[1-hydroxy-1-(pyrimidin-2-yl)methyl]-indoline



2-Tributylstannylpyridine (0.2 g) synthesized in accordance with the method described in J. Am. Chem. Soc., 1481 (1978). and 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-formylindoline (0.21 g) were treated in accordance with the method described in Tetrahedron Lett., 275 (1994). to give the title compound (0.038 g) as a yellow oil (yield: 16.2%).

Next, oxalic acid (8 mg) was added thereto to give the oxalate of the title compound as an amorphous solid.

m.p. (oxalate): 123°C.

Oxalate

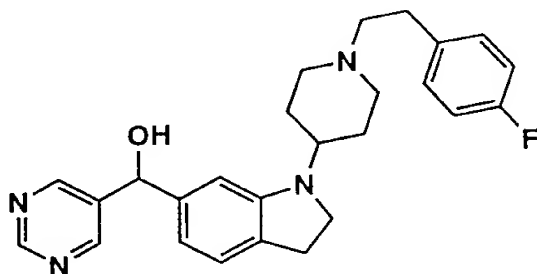
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.84(4H, m), 2.82(2H, t, J=8.2Hz), 2.98(2H, m), 3.04(2H, m), 3.19(2H, m), 3.29(2H, t, J=8.2Hz), 3.58(2H, m), 3.68(1H, m), 5.65(1H, s), 6.60(1H, d, J=7.2Hz), 6.65(1H, s),

6.91 (1H, d, J=7.2Hz), 7.18 (2H, m), 7.33 (2H, m), 7.36 (1H, t, J=4.8Hz), 8.76 (2H, d, J=4.8Hz).

ESI-Mass: 433.3 (MH+).

Example 198: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[1-hydroxy-1-(pyrimidin-5-yl)methyl]-indoline



5-Bromopyridine (1.27 g) and 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-formylindoline (0.21 g) were treated in accordance with the method described in Synth. Commun., 253 (1994). to give the title compound (0.624 g) as a pale yellow oil (yield: 36.1%).

Next, oxalic acid (32 mg) was added to 0.156 g of the above product to give the oxalate of the title compound as a hygroscopic amorphous solid.

Oxalate

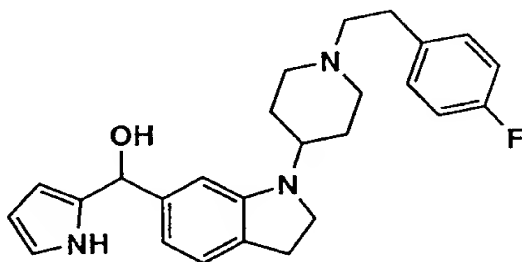
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.78-1.92 (4H, m), 2.84 (2H, t, J=8.4Hz), 2.95 (4H, m), 3.13 (2H, m), 3.23 (2H, t, J=8.2Hz), 3.51 (2H, m), 3.68 (1H, m), 5.71 (1H, s), 6.59 (1H, d, J=7.0Hz), 6.60 (1H, s), 6.97 (1H,

d, J=7.0Hz), 7.17 (2H, m), 7.33 (2H, m), 8.75 (2H, s), 9.04 (1H, s).

FAB-Mass: 433 (MH+).

Example 199: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-[1-hydroxy-1-(2-pyrrolyl)methyl]indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-bromoindoline (0.2 g) and 2-pyrrolicarboxyaldehyde (0.44 ml) were treated as in Example 193 to give the title compound (0.044 g) as a colorless oil (yield: 21.0%).

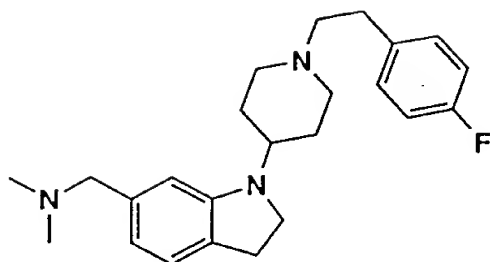
Free

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.80 (4H, m), 2.14 (2H, m), 2.60 (2H, m), 2.81 (2H, m), 2.94 (2H, t, J=8.4Hz), 3.12 (2H, br-d), 3.38 (1H, m), 3.42 (2H, t, J=8.4Hz), 5.79 (1H, s), 6.03 (1H, m), 6.13 (1H, m), 6.50 (1H, d, J=1.2Hz), 6.62 (1H, dd, J=1.2, 7.2Hz), 6.71 (1H, m), 6.97 (2H, m), 7.02 (1H, d, J=7.2Hz), 7.15 (2H, m), 8.33 (1H, m).

Fab-Mass: 420 (MH+).

Example 200: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-N,N-dimethylaminomethylindoline



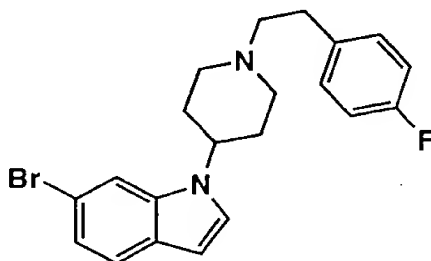
1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-amino-
methyllindoline (500 mg), formaldehyde (290 mg) and formic acid
(180 mg) were treated as in Example 170 to give the hydrochloride
(60 mg) of the title compound as a pale brown hygroscopic
amorphous solid (yield: 9.3%).

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6):

δ (ppm) 1.94-2.03 (2H, m), 2.04-2.17 (2H, m), 2.66 (3H, s),
2.67 (3H, s), 2.92 (2H, t, $J=8\text{Hz}$), 3.00-3.12 (4H, m), 3.26-3.35 (2H,
m), 3.39 (2H, t, $J=8\text{Hz}$), 3.58-3.70 (3H, m), 4.12 (2H, s), 6.65 (1H,
d, $J=8\text{Hz}$), 6.93 (1H, s), 7.08 (1H, d, $J=8\text{Hz}$), 7.16-7.21 (2H, m),
7.32-7.36 (2H, m), 10.52 (1H, br-s), 10.62 (1H, br-s).

FAB-Mass: 382 (MH+).

Example 201-1: Synthesis of 1-[1-(4-fluorophenethyl)-
piperidin-4-yl]-6-bromoindole



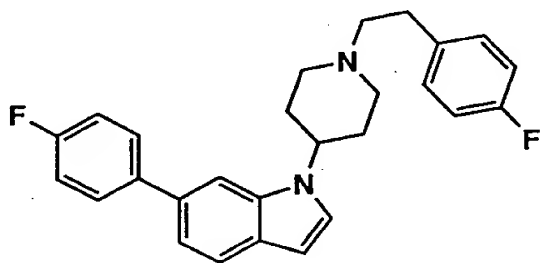
1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-

bromoindoline (0.1 g) was dissolved in chloroform (27 ml). After adding manganese dioxide (2.75 g), the resultant mixture was heated under reflux for 4 hr. Then manganese dioxide was filtered off and the filtrate was concentrated under reduced pressure to give the title compound (0.480 g) as a yellow oil (yield: 96.5%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 2.09(4H, m), 2.25(2H, m), 2.50(2H, m), 2.82(2H, m), 3.17(2H, br-d), 4.17(1H, m), 6.49(1H, d, J=2.8Hz), 6.99(2H, m), 7.18(2H, m), 7.20(1H, d, J=8.4Hz), 7.21(1H, d, J=2.8Hz), 7.48(1H, d, J=8.4Hz), 7.53(1H, br-s).

Example 201-2: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(4-fluorophenyl)indole



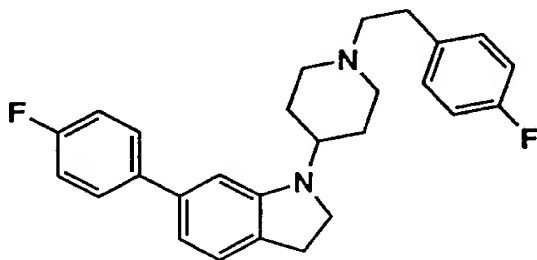
1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-bromoindole (0.1 g), 4-fluorophenylboronic acid (0.067 g), tetraquistriphenylphosphine palladium (0.014 g) and sodium carbonate (0.12 g) were dissolved in toluene (5 ml) and water (1.2 ml) and the resultant solution was stirred at 90°C for 12

hr. After filtering the reaction mixture, ethyl acetate and a saturated aqueous solution of sodium bicarbonate were added to the filtrate and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Then the residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (0.075 g) as pale yellow crystals (yield: 71.6%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 2.19 (4H, m), 2.42 (2H, m), 2.75 (2H, m), 2.89 (2H, m), 3.27 (2H, m), 4.33 (1H, m), 6.51 (1H, d, J=2.4Hz), 6.98 (2H, m), 7.14 (6H, m), 7.30 (1H, dd, J=1.4, 8.0Hz), 7.44 (1H, s), 7.59 (2H, m), 7.67 (1H, d, J=8.0Hz).

Example 201-3: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(4-fluorophenyl)indoline



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-(4-fluorophenyl)indole (0.075 g) was treated as in Production Example 56-2 to give the title compound (0.020 g) as a yellow oil (yield: 26.6%).

Next, oxalic acid was added thereto to give the oxalate

of the title compound.

m.p. (oxalate): 130 - 145°C.

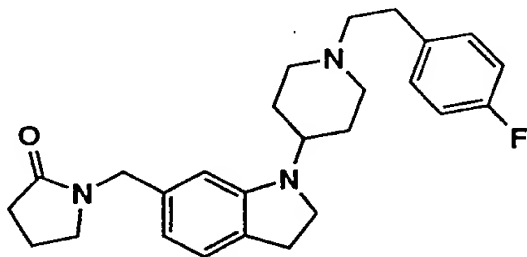
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.93(2H, m), 2.08(2H, m), 2.93(2H, t, J=8.2Hz), 3.10(4H, m), 3.25(2H, m), 3.39(2H, t, J=8.2Hz), 3.64(2H, m), 3.89(1H, m), 6.77(1H, s), 6.82(1H, d, J=7.4Hz), 7.00(1H, d, J=7.4Hz), 7.19(2H, m), 7.25(2H, m), 7.34(2H, m), 7.65(2H, m).

FAB-Mass: 417(MH⁺).

Example 202: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(2-pyrrolidone-1-yl)methylindoline



60% Sodium hydride (40 mg) was added to a solution of 2-pyrrolidone (85 mg) in dimethylformamide (10 ml) and the resultant mixture was stirred at 50°C for 2 hr. Next, 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-chloromethylindoline (200 mg) was added thereto and the resultant mixture was stirred for additional 2 hr. Then ethyl acetate and water were added to the reaction solution and the layers were separated. The organic layer was washed with brine,

dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/ethanol system) followed by conversion into a hydrochloride in a conventional manner to give the hydrochloride (170 mg) of the title compound as a purple powder (yield: 69%).

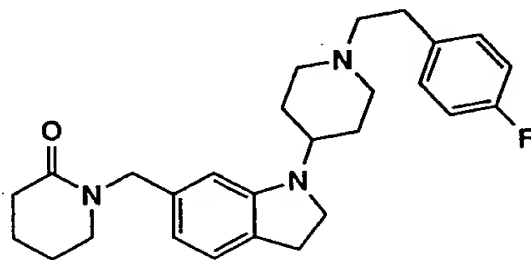
m.p. (hydrochloride): 140 - 142°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.81-1.92 (4H, m), 1.94-2.08 (2H, m), 2.25 (2H, t, J=8Hz), 2.81-2.87 (2H, m), 3.00-3.35 (10H, m), 3.57-3.74 (3H, m), 4.22 (2H, s), 6.35 (1H, s), 6.40 (1H, d, J=8Hz), 6.96 (1H, d, J=8Hz), 7.14-7.19 (2H, m), 7.30-7.34 (2H, m).

FAB-Mass: 422 (MH⁺).

Example 203: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(2-piperidon-1-yl)methylindoline



2-Piperidone (64 mg), 60% sodium hydride (26 mg) and 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-chloromethylindoline (200 mg) were treated as in Example 202 to give the hydrochloride (130 mg) of the title compound as a

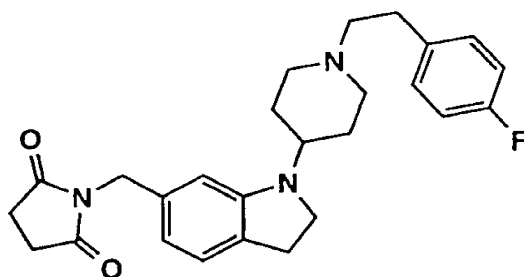
dark red hygroscopic amorphous solid (yield: 51%).

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6):

$\delta(\text{ppm})$ 1.60-1.73 (4H, m), 1.82-1.89 (2H, m), 2.02-2.15 (2H, m), 2.26-2.32 (2H, m), 2.87 (2H, t, $J=8\text{Hz}$), 3.04-3.16 (6H, m), 3.21-3.28 (2H, m), 3.34 (2H, t, $J=8\text{Hz}$), 3.60-3.70 (2H, m), 4.40 (2H, s), 6.41 (1H, s), 6.45 (1H, d, $J=8\text{Hz}$), 6.98 (1H, d, $J=8\text{Hz}$), 7.16-7.21 (2H, m), 7.32-7.36 (2H, m).

FAB-Mass: 436 (MH+).

Example 204: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(succinimido-1-yl)methylindoline



Succinimide (64 mg), 60% sodium hydride (26 mg) and 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-chloromethylindoline (200 mg) were treated as in Example 202 to give the hydrochloride (140 mg) of the title compound as a dark purple hygroscopic amorphous solid (yield: 55%).

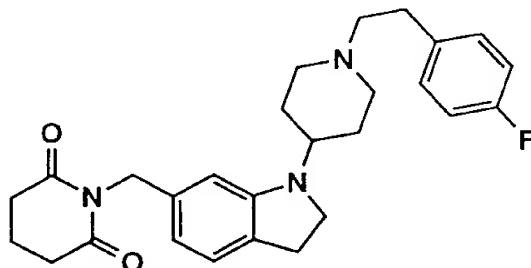
$^1\text{H-NMR}$ (400 MHz, DMSO-d_6):

$\delta(\text{ppm})$ 1.84-2.05 (4H, m), 2.67 (4H, s), 2.85 (2H, t, $J=8\text{Hz}$), 3.02-3.20 (4H, m), 3.24-3.35 (4H, m), 3.60-3.75 (3H, m), 4.43 (2H, s), 6.41-6.44 (2H, m), 6.94 (1H, d, $J=8\text{Hz}$), 7.17-7.22 (2H, m),

7.32-7.37 (2H, m).

FAB-Mass: 436 (MH+).

Example 205: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(glutarimido-1-yl)methylindoline



Glutarimide (73 mg), 60% sodium hydride (26 mg) and 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-chloromethylindoline (200 mg) were treated as in Example 202 to give the oxalate (240 mg) of the title compound as a pale brown powder (yield: 82%).

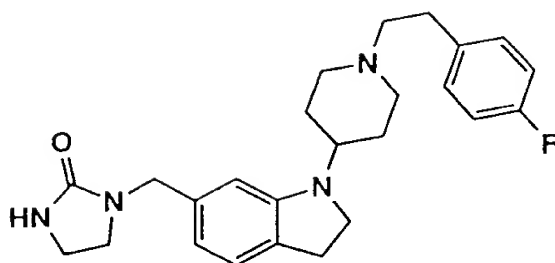
m.p. (oxalate): 109 - 111°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.80-1.91 (6H, m), 2.65 (4H, t, J=6Hz), 2.83 (2H, t, J=8Hz), 2.92-3.04 (4H, m), 3.12-3.22 (2H, m), 3.31 (2H, t, J=8Hz), 3.49-3.71 (3H, m), 4.72 (2H, s), 6.35-6.37 (2H, m), 6.91 (1H, d, J=8Hz), 7.15-7.20 (2H, m), 7.31-7.35 (2H, m).

FAB-Mass: 450 (MH+).

Example 206: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(2-imidazolidonyl)methylindoline



2-Imidazolidone (60 mg), 60% sodium hydride (28 mg) and 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-chloromethylindoline (260 mg) were treated as in Example 202 to give the oxalate (120 mg) of the title compound as white prisms (yield: 33%).

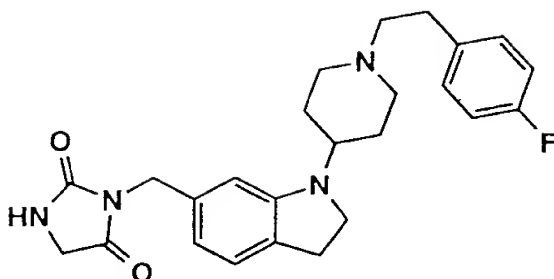
m.p. (oxalate): 184 - 186°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.80-1.89 (4H, m), 2.86 (2H, t, J=8Hz), 2.90-2.99 (4H, m), 3.08-3.24 (6H, m), 3.33 (2H, t, J=8Hz), 3.47-3.55 (2H, m), 3.60-3.68 (1H, m), 4.10 (2H, s), 6.34-6.37 (2H, m), 6.43 (1H, d, J=8Hz), 6.97 (1H, d, J=8Hz), 7.15-7.19 (2H, m), 7.31-7.34 (2H, m).

FAB-Mass: 423 (MH⁺).

Example 207: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(2,4-imidazolidinedion-3-yl)methylindoline



Hydantoin (130 mg), 60% sodium hydride (54 mg) and 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-chloromethylindoline (400 mg) were treated as in Example 202 to give the title compound (230 mg) as a white powder (yield: 49%).

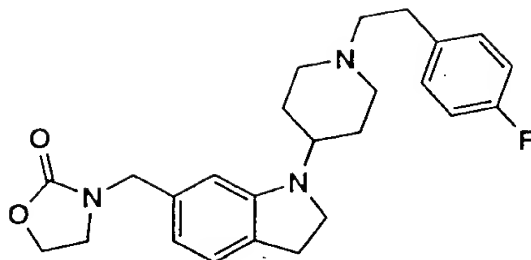
m.p.: 191 - 193°C.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.68-1.84 (4H, m), 2.11-2.21 (2H, m), 2.56-2.63 (2H, m), 2.76-2.83 (2H, m), 2.90 (2H, t, J=8Hz), 3.06-3.15 (2H, m), 3.39 (2H, t, J=8Hz), 3.35-3.46 (1H, m), 3.92 (2H, s), 4.57 (2H, s), 5.90 (1H, s), 6.47 (1H, s), 6.65 (1H, d, J=8Hz), 6.94-7.00 (3H, m), 7.13-7.19 (2H, m).

FAB-Mass: 436 (MH⁺).

Example 208: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(2-oxazolidon-3-yl)methylindoline



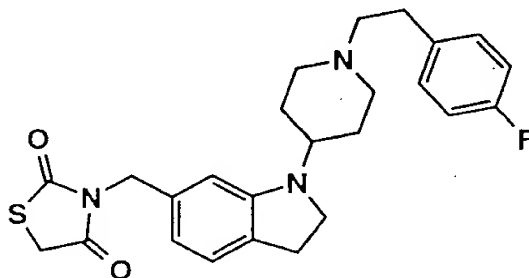
2-Oxazolidone (120 mg), 60% sodium hydride (54 mg) and 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-chloromethylindoline (400 mg) were treated as in Example 202 to give the hydrochloride (450 mg) of the title compound as a pale red hygroscopic amorphous solid (yield: 92%).

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6):

δ (ppm) 1.82-1.90 (2H, m), 2.05-2.18 (2H, m), 2.89 (2H, t, $J=8\text{Hz}$), 3.03-3.15 (4H, m), 3.19-3.28 (2H, m), 3.31-3.80 (7H, m), 4.21-4.29 (4H, m), 6.44-6.50 (2H, m), 7.01 (1H, d, $J=8\text{Hz}$), 7.16-7.21 (2H, m), 7.32-7.36 (2H, m).

FAB-Mass: 424 (MH+).

Example 209: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(2,4-thiazolidinedion-3-yl)methylindoline



2,4-Thiazolidinedione (110 mg), 60% sodium hydride (40

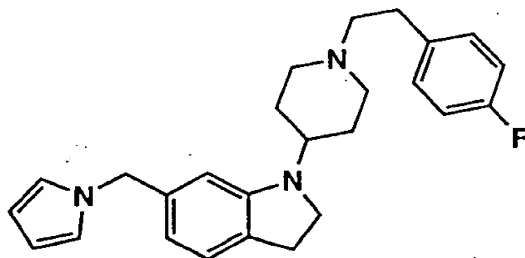
mg) and 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-chloromethylindoline (300 mg) were treated as in Example 202 to give the hydrochloride (120 mg) of the title compound as a red hygroscopic amorphous solid (yield: 30%).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.83-2.06 (4H, m), 2.86 (2H, t, J=8Hz), 3.10-3.19 (4H, m), 3.24-3.35 (4H, m), 3.60-3.76 (3H, m), 4.27 (2H, s), 4.56 (2H, s), 6.43-6.45 (2H, m), 6.97 (1H, d, J=8Hz), 7.17-7.22 (2H, m), 7.32-7.36 (2H, m).

FAB-Mass: 454 (MH⁺).

Example 210: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(pyrrol-1-yl)methylindoline



Pyrrole (50 mg), 60% sodium hydride (30 mg) and 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-chloromethylindoline (250 mg) were treated as in Example 202 to give the hydrochloride (240 mg) of the title compound as a brown powder (yield: 82%).
m.p. (hydrochloride): 162°C (decomp.).

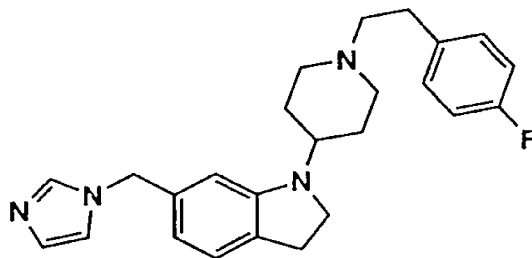
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.80-1.87 (2H, m), 2.06-2.19 (2H, m), 2.84 (2H, t,

J=8Hz), 2.99-3.12 (4H, m), 3.18-3.25 (2H, m), 3.33 (2H, t, J=8Hz), 3.56-3.70 (3H, m), 4.92 (2H, s), 5.94-5.96 (2H, m), 6.41 (1H, d, J=8Hz), 6.52 (1H, s), 6.75-6.77 (2H, m), 6.95 (1H, d, J=8Hz), 7.14-7.19 (2H, m), 7.29-7.34 (2H, m), 11.06 (1H, br-s).

FAB-Mass: 405 (MH+).

Example 211: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(imidazol-1-yl)methylindoline



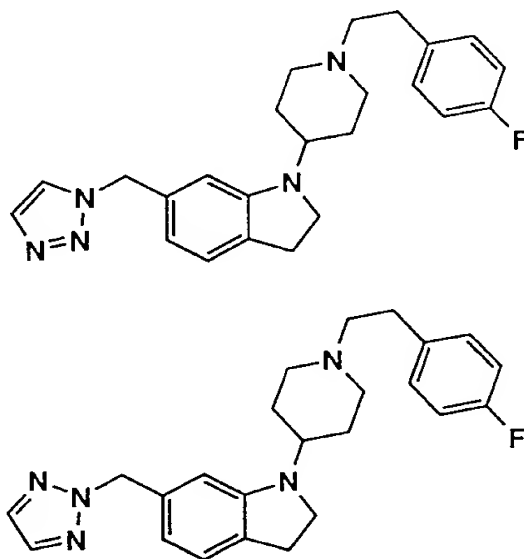
Imidazole (50 mg), 60% sodium hydride (30 mg) and 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-chloromethylindoline (250 mg) were treated as in Example 202 to give the hydrochloride (260 mg) of the title compound as a red hygroscopic amorphous solid (yield: 88%).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.81-1.90 (2H, m), 2.15-2.28 (2H, m), 2.86 (2H, t, J=8Hz), 2.99-3.14 (4H, m), 3.21-3.29 (2H, m), 3.36 (2H, t, J=8Hz), 3.58-3.68 (3H, m), 5.25 (2H, s), 6.59 (1H, d, J=8Hz), 6.81 (1H, s), 7.01 (1H, d, J=8Hz), 7.14-7.19 (2H, m), 7.30-7.34 (2H, m), 7.66 (1H, s), 7.82 (1H, s), 11.07 (1H, br-s).

FAB-Mass: 405 (MH+).

Example 212: Synthesis of 1-[1-(4-fluorophenethyl)-
piperidin-4-yl]-6-(1,2,3-triazol-1-yl)methylindoline and 1-
[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1,2,3-triazol-2-
yl)methylindoline



1,2,3-Triazole (51 mg), 60% sodium hydride (30 mg) and 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-chloromethylindoline (250 mg) were treated as in Example 202 to give the hydrochloride (180 mg) of highly polar 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1,2,3-triazol-1-yl)methylindoline as a dark red hygroscopic amorphous solid (yield: 61%), and also the hydrochloride (40 mg) of lowly polar 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1,2,3-triazol-2-yl)methylindoline as a pale red hygroscopic amorphous solid (yield: 14%).

(1) 1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-(1,2,3-

triazol-1-yl)methylindoline (highly polar)

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.80-1.88 (2H, m), 2.05-2.18 (2H, m), 2.87 (2H, t, J=8Hz), 3.02-3.14 (4H, m), 3.21-3.30 (2H, m), 3.34 (2H, t, J=8Hz), 3.60-3.75 (3H, m), 5.46 (2H, s), 6.51 (1H, d, J=8Hz), 6.57 (1H, s), 7.00 (1H, d, J=8Hz), 7.16-7.21 (2H, m), 7.32-7.40 (2H, m), 7.73 (1H, s), 8.17 (1H, s), 10.88 (1H, br-s).

FAB-Mass: 406 (MH⁺).

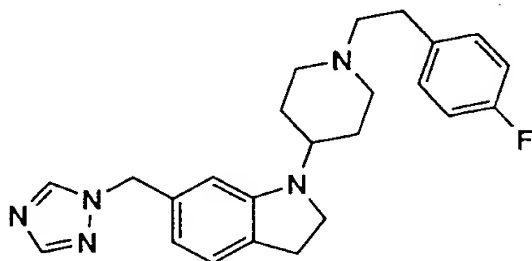
(2) 1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-(1,2,3-triazol-2-yl)methylindoline (lowly polar)

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.81-1.90 (2H, m), 1.94-2.10 (2H, m), 2.86 (2H, t, J=8Hz), 3.01-3.18 (4H, m), 3.22-3.30 (2H, m), 3.33 (2H, t, J=8Hz), 3.60-3.75 (3H, m), 5.49 (2H, s), 6.45 (1H, d, J=8Hz), 6.48 (1H, s), 6.98 (1H, d, J=8Hz), 7.17-7.22 (2H, m), 7.32-7.36 (2H, m), 7.78 (2H, s).

FAB-Mass: 406 (MH⁺).

Example 213: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(1,2,4-triazol-2-yl)methylindoline



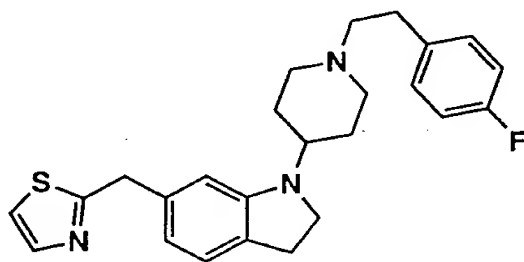
1,2,4-Triazole (51 mg), 60% sodium hydride (30 mg) and 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-chloromethyl-indoline (250 mg) were treated as in Example 202 to give the hydrochloride (210 mg) of the title compound as a brown hygroscopic amorphous substance (yield: 71%).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.81-1.90(2H, m), 1.95-2.14(2H, m), 2.87(2H, t, J=8Hz), 3.01-3.15(4H, m), 3.21-3.32(2H, m), 3.34(2H, t, J=8Hz), 3.60-3.74(3H, m), 5.27(2H, s), 6.48(1H, d, J=8Hz), 6.50-6.59(1H, m), 6.99(1H, d, J=8Hz), 7.17-7.22(2H, m), 7.32-7.40(2H, m), 7.97-8.00(1H, m), 8.64-8.72(1H, m).

FAB-Mass: 406(MH+).

Example 214: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-(2-thiazolyl)methylindoline



A mixture of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-thiocarbamoylmethylindoline (150 mg), 40% chloroacetaldehyde (300 mg), potassium carbonate (79 mg) and dimethoxyethane (32 ml) was stirred overnight. Then the liquid reaction mixture was filtered and the filtrate was concentrated

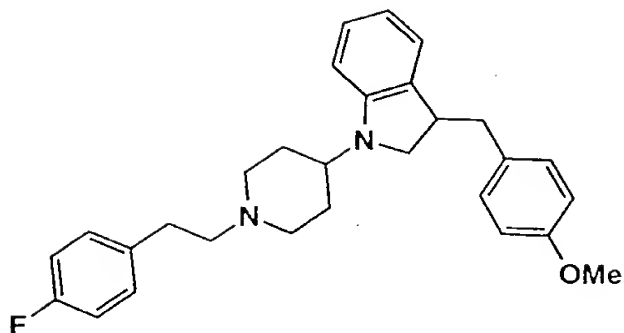
under reduced pressure. To the residue were added trifluoroacetic anhydride (240 mg), pyridine (210 mg) and dimethoxyethane (4 ml) and the resultant mixture was stirred for 30 min. Then the reaction solution was concentrated under reduced pressure and diluted with a saturated aqueous solution of sodium bicarbonate and ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) followed by conversion into a hydrochloride in a conventional manner to give the hydrochloride (40 mg) of the title compound as a brown hygroscopic amorphous solid (yield: 23%).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.82-1.90 (2H, m), 2.03-2.15 (2H, m), 2.88 (2H, t, J=8Hz), 3.03-3.15 (4H, m), 3.20-3.28 (2H, m), 3.35 (2H, t, J=8Hz), 3.58-3.66 (2H, m), 3.68-3.80 (1H, m), 4.23 (2H, s), 6.55 (1H, d, J=8Hz), 6.57 (1H, s), 6.99 (1H, d, J=8Hz), 7.16-7.21 (2H, m), 7.31-7.35 (2H, m), 7.60 (1H, s), 7.75 (1H, s), 10.82 (1H, br-s).

FAB-Mass: 422 (MH⁺).

Example 215: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-3-(4-methoxybenzyl)indoline



3-(4-Methoxybenzyl)indoline (0.2 g) and 1-(4-fluorophenethyl)-4-piperidone (0.262 g) were treated as in Example 16 to give the title compound (0.343 g) as a colorless oil (yield: 94.9%).

Next, oxalic acid (36 mg) was added thereto to give the oxalate (0.101 g) of the title compound as colorless crystals. m.p. (oxalate): 187°C.

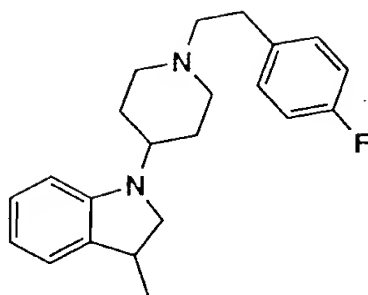
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.80(4H, m), 2.63(1H, dd, J=9.0, 13.6Hz), 2.96(4H, m), 3.15(4H, m), 3.27(1H, t, J=8.6Hz), 3.43(1H, m), 3.52(2H, m), 3.67(1H, m), 3.74(3H, s), 6.52(1H, d, J=7.6Hz), 6.55(1H, t, J=7.6Hz), 6.87(2H, d, J=8.4Hz), 6.92(1H, d, J=7.6Hz), 7.01(1H, t, J=7.6Hz), 7.16(2H, d, J=8.4Hz), 7.18(2H, d, J=8.4Hz), 7.32(2H, dd, J=6.0, 8.4Hz).

ESI-Mass: 445.3(MH⁺).

Example 216: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-3-methylindoline



3-Methylindoline (0.2 g) and 1-(4-fluorophenethyl)-4-piperidone (0.50 g) were treated as in Example 16 to give the title compound (0.384 g) as a pale yellow oil (yield: 70.7%).

Next, hydrochloric acid was added thereto to give a salt followed by recrystallization from ethanol. Thus the hydrochloride (0.314 g) of the title compound was obtained as colorless crystals.

m.p. (hydrochloride): 232°C.

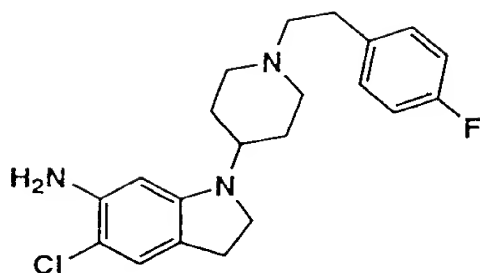
Hydrochloride

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.25(3H, d, J=6.8Hz), 1.89(2H, m), 2.33(2H, m), 2.88(1H, t, J=8.0Hz), 3.10(4H, m), 3.23(3H, m), 3.55(1H, t, J=8.0Hz), 3.61(2H, m), 3.78(1H, m), 6.67(2H, m), 7.06(2H, m), 7.18(2H, t, J=8.8Hz), 7.33(2H, m).

ESI-Mass: 339.2(MH⁺).

Example 217: 1-[1-(4-fluorophenethyl)piperidin-4-yl]-5-chloro-6-aminoindoline

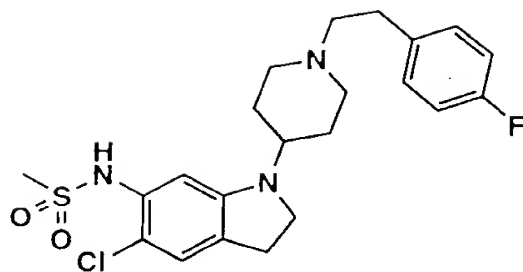


N-Chlorosuccinimide (0.24 g) was added at room temperature to a solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminoindoline (0.5 g) in acetonitrile (50 ml) and the resultant mixture was stirred for 1 hr. Then the reaction mixture was filtered and concentrated under reduced pressure. Next, a 5 N aqueous solution of sodium hydroxide and ethyl acetate were added thereto and the layers were separated. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The resulting residue was purified by silica gel column chromatography (methylene chloride/ethanol system) to give the title compound (0.19 g) as a brown oil (yield: 34%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.69-1.83(4H, m), 2.03-2.11(2H, m), 2.51-2.60(2H, m), 2.75-2.82(2H, m), 2.83(2H, t, J=8Hz), 3.08-3.15(2H, m), 3.20-3.32(1H, m), 3.38(2H, t, J=8Hz), 3.85(2H, br-s), 5.89(1H, s), 6.89(1H, s), 6.92-7.00(2H, m), 7.11-7.21(2H, m).

Example 218: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-5-chloro-6-methanesulfonylaminoindoline



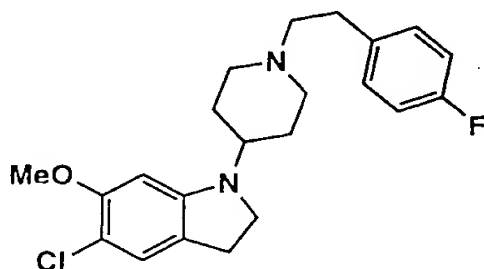
1-[1-(4-Fluorophenethyl)piperidin-4-yl]-5-chloro-6-aminindoline (0.19 g) and methanesulfonyl chloride (0.058 g) were treated as in Example 116 to give the oxalate (160 mg) of the title compound as a pale red powder (yield: 58%).
m.p. (oxalate): 193 - 196°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.73-1.83 (4H, m), 2.81-3.00 (6H, m), 2.91 (3H, s), 3.09-3.15 (2H, m), 3.37 (2H, t, J=8Hz), 3.42-3.56 (2H, m), 3.58-3.65 (1H, m), 6.49 (1H, s), 7.10 (1H, s), 7.12-7.20 (2H, m), 7.23-7.31 (2H, m).

FAB-Mass: 452 (MH⁺).

Example 219: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-5-chloro-6-methoxyindoline



N-Chlorosuccinimide (0.15 g) was added at room temperature

to a solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methoxyindoline (0.39 g) in methylene chloride (5 ml) and the resultant mixture was stirred for 20 min. Then a 5 N aqueous solution of sodium hydroxide and ethyl acetate were added to the reaction solution and the layers were separated. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The resulting residue was purified by silica gel column chromatography (methylene chloride/ethanol system) followed by conversion into a hydrochloride to give the hydrochloride (0.10 g) of the title compound as a pale red powder (yield: 21%).

m.p. (hydrochloride): 135 - 138°C.

¹H-NMR (400 MHz, DMSO-d₆):

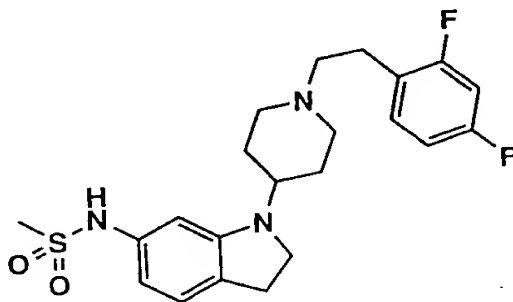
δ(ppm) 1.83-2.08 (4H, m), 2.82 (2H, t, J=8Hz), 3.00-3.12 (4H, m), 3.21-3.29 (2H, m), 3.34 (2H, t, J=8Hz), 3.60-3.67 (2H, m), 3.72-3.84 (1H, m), 3.79 (3H, s), 6.34 (1H, s), 6.99 (1H, s), 7.15-7.20 (2H, m), 7.30-7.34 (2H, m).

FAB-Mass: 399 (MH+).

Example 220: Synthesis of 1-[1-(2,4-difluorophenethyl)-piperidin-4-yl]-6-aminoindoline

Nc1ccc2c(c1)c(c[nH]2)C3CCCCN3CCc4cc(F)cc(F)c4 $^1\text{H-NMR}$ (400 MHz, CDCl_3):

Example 221: Synthesis of 1-[1-(2,4-difluorophenethyl)-piperidin-4-yl]-6-methanesulfonylaminoindoline



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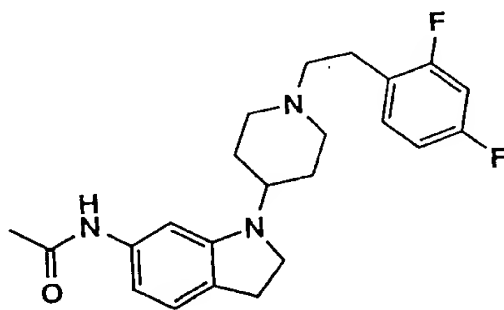
solid (yield: 45%).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.83-1.89 (2H, m), 1.99-2.10 (2H, m), 2.84 (2H, t, J=8Hz), 2.89 (3H, s), 3.05-3.27 (6H, m), 3.33 (2H, t, J=8Hz), 3.35-3.43 (1H, m), 3.59-3.68 (2H, m), 6.38-6.41 (2H, m), 6.94 (1H, d, J=8Hz), 7.06-7.11 (1H, m), 7.22-7.28 (1H, m), 7.39-7.45 (1H, m), 9.34 (1H, br-s), 10.76 (1H, br-s).

FAB-Mass: 436 (MH⁺)

Example 222: Synthesis of 1-[1-(2,4-difluorophenethyl)-piperidin-4-yl]-6-acetamidoindoline



1-[1-(2,4-Difluorophenethyl)piperidin-4-yl]-6-

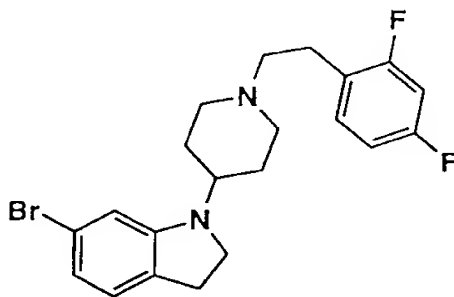
aminoindoline (0.6 g) and acetic anhydride (5 ml) were treated as in Example 133 to give the hydrochloride (640 mg) of the title compound as a white powder (yield: 87%).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.83-1.98 (4H, m), 1.99 (3H, s), 2.81 (2H, t, J=8Hz), 3.00-3.13 (4H, m), 3.22-3.33 (4H, m), 3.55-3.69 (3H, m), 6.58 (1H, d, J=8Hz), 6.90 (1H, d, J=8Hz), 6.95 (1H, s), 7.07-7.12 (1H, m), 7.24-7.30 (1H, m), 7.39-7.45 (1H, m), 9.69 (1H, br-s).

FAB-Mass: 400 (MH⁺) .

Example 223: Synthesis of 1-[1-(2,4-difluorophenethyl)-piperidin-4-yl]-6-bromoindoline

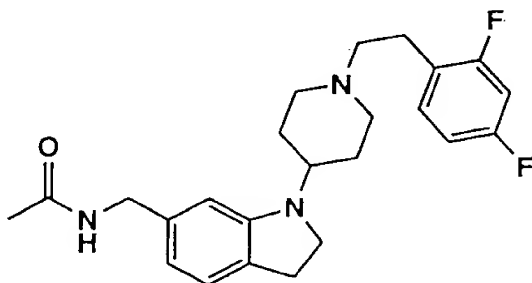


1-(Piperidin-4-yl)-6-bromoindoline (3.0 g) and 2,4-difluorophenethyl bromide (3.1 g) were treated as in Example 2 to give the title compound (2.7 g) as a white powder (yield: 60%) .

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.70-1.85 (4H, m) , 2.10-2.21 (2H, m) , 2.51-2.63 (2H, m) , 2.79-2.89 (2H, m) , 2.90 (2H, t, J=8Hz) , 3.08-3.17 (2H, m) , 3.28-3.37 (1H, m) , 3.41 (2H, t, J=8Hz) , 6.48 (1H, s) , 6.69 (1H, d, J=8Hz) , 6.72-6.84 (2H, m) , 6.90 (1H, d, J=8Hz) , 7.11-7.20 (1H, m) .

Example 224: Synthesis of 1-[1-(2,4-difluorophenethyl)-piperidin-4-yl]-6-acetamidomethylindoline



1-[1-(2,4-Difluorophenethyl)piperidin-4-yl]-6-bromoindoline (3.5 g) was treated as in Examples 130 to 133 to give the hydrochloride (0.26 g) of the title compound as a gray powder (yield: 7.3%).

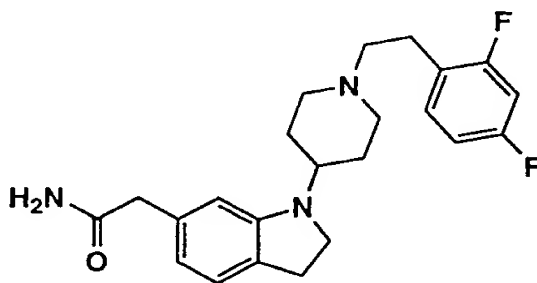
m.p. (hydrochloride): 179°C (decomp.)

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.80 (3H, s), 1.85-2.05 (4H, m), 2.90 (2H, t, J=8Hz), 3.03-3.28 (4H, m), 3.21-3.39 (4H, m), 3.64-3.78 (3H, m), 4.30 (2H, s), 6.51-6.60 (2H, m), 6.98-7.08 (2H, m), 7.11-7.19 (1H, m), 7.32-7.40 (1H, m), 8.25 (1H, br-s).

FAB-Mass: 414 (MH⁺).

Example 225: Synthesis of 1-[1-(2,4-difluorophenethyl)-piperidin-4-yl]-6-carbamoylmethylindoline



1-[1-(2,4-Difluorophenethyl)piperidin-4-yl]-6-bromoindoline (1.8 g) was treated as in Examples 136, 142, 145 and 147 to give the hydrochloride (0.12 g) of the title compound as a pale green powder (yield: 6.6%).

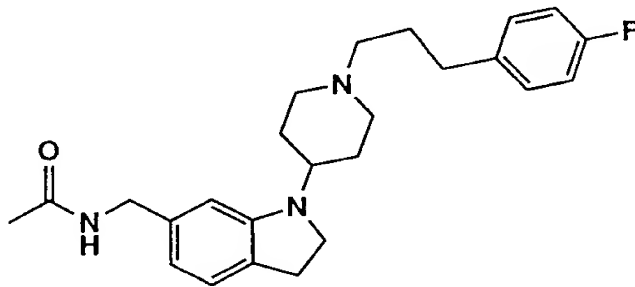
m.p. (hydrochloride): 241 - 243°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ (ppm) 1.85-2.05 (4H, m), 2.89 (2H, t, J=8Hz), 3.03-3.18 (4H, m), 3.21-3.43 (4H, m), 3.49 (2H, s), 3.64-3.77 (3H, m), 6.52-6.59 (2H, m), 6.98-7.10 (4H, m), 7.29-7.35 (1H, m), 7.59 (1H, br-s).

FAB-Mass: 400 (MH+).

Example 226: Synthesis of 1-{1-[3-(4-fluorophenyl)-propyl]piperidin-4-yl}-6-acetamidomethylindoline



1-(Piperidin-4-yl)-6-acetamidomethylindoline (250 mg) and 3-(4-fluorophenyl)propyl bromide (240 mg) were treated as in Example 2 to give the title compound (220 mg) as pale yellow prisms (yield: 58%).

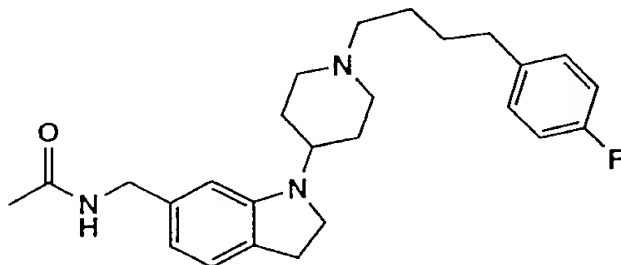
m.p.: 128 - 130°C.

$^1\text{H-NMR}$ (400 MHz, CDCl_3):

δ (ppm) 1.73-1.99 (6H, m), 2.00 (3H, s), 2.02-2.20 (2H, m), 2.39-2.67 (4H, m), 2.92 (2H, t, J=8Hz), 3.02-3.20 (2H, m), 3.34-3.44 (1H, m), 3.41 (2H, t, J=8Hz), 4.32 (2H, d, J=6Hz), 5.71 (1H, br-s), 6.33 (1H, s), 6.45 (1H, d, J=8Hz), 6.94-7.00 (3H, m), 7.12-7.16 (2H, m).

FAB-Mass: 410 (MH+).

Example 227: Synthesis of 1-[1-[4-(4-fluorophenyl)butyl]-piperidin-4-yl]-6-acetamidomethylindoline



1-(Piperidin-4-yl)-6-acetamidomethylindoline (250 mg) and 4-(4-fluorophenyl)butyl bromide (250 mg) were treated as in Example 2 to give the title compound (280 mg) as white needles (yield: 70%).

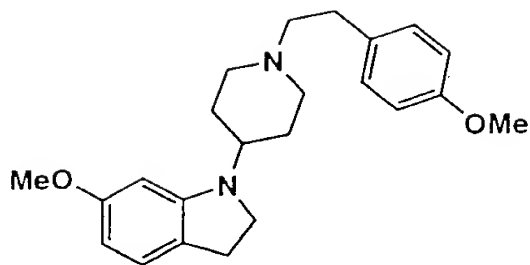
m.p.: 119 - 121°C.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.50-1.68 (4H, m), 1.70-1.84 (4H, m), 1.99-2.12 (2H, m), 2.00 (3H, s), 2.34-2.45 (2H, m), 2.57-2.64 (2H, m), 2.91 (2H, t, J=8Hz), 3.00-3.10 (2H, m), 3.32-3.44 (1H, m), 3.40 (2H, t, J=8Hz), 4.32 (2H, d, J=6Hz), 5.70 (1H, br-s), 6.31 (1H, s), 6.59 (1H, d, J=8Hz), 6.93-7.00 (3H, m), 7.10-7.14 (2H, m).

FAB-Mass: 424 (MH⁺).

Example 228: Synthesis of 1-[1-(4-methoxyphenethyl)-piperidin-4-yl]-6-methoxyindoline



1-(Piperidin-4-yl)-6-methoxyindoline (320 mg) and 4-methoxyphenethyl bromide (360 mg) were treated as in Example 2 to give the oxalate (220 mg) of the title compound as a white powder (yield: 34%).

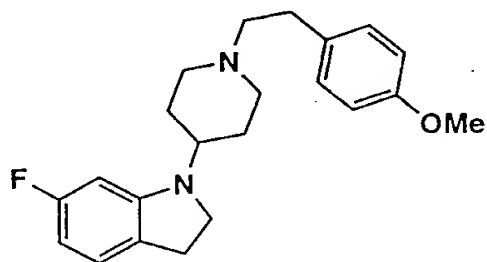
m.p. (oxalate): 165 - 167°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.74-1.88 (4H, m), 2.79 (2H, t, J=8Hz), 2.84-2.90 (4H, m), 3.03-3.12 (2H, m), 3.30 (2H, t, J=8Hz), 3.47-3.69 (3H, m), 3.67 (3H, s), 3.71 (3H, s), 6.07-6.15 (2H, m), 6.84-6.93 (3H, m), 7.16-7.21 (2H, m).

FAB-Mass: 367 (MH⁺).

Example 229: Synthesis of 1-[1-(4-methoxyphenethyl)-piperidin-4-yl]-6-fluoroindoline



1-(Piperidin-4-yl)-6-fluoroindoline (250 mg) and 4-

methoxyphenethyl bromide (290 mg) were treated as in Example 2 to give the hydrochloride (120 mg) of the title compound as a white powder (yield: 27%).

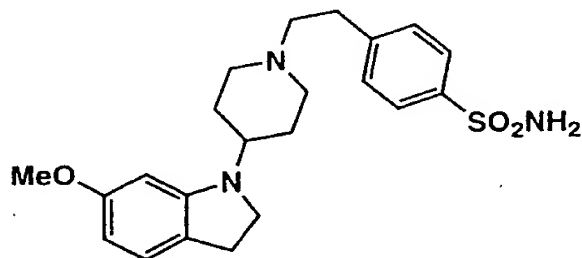
m.p. (hydrochloride): 212 - 214°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.83-1.92 (4H, m), 2.83 (2H, t, J=8Hz), 2.90-2.97 (2H, m), 3.00-3.10 (2H, m), 3.17-3.26 (2H, m), 3.38 (2H, t, J=8Hz), 3.60-3.73 (3H, m), 3.72 (3H, s), 6.24-6.29 (1H, m), 6.36-6.40 (1H, m), 6.87-6.97 (3H, m), 7.17-7.21 (2H, m).

FAB-Mass: 355 (MH+).

Example 230: Synthesis of 1-[1-(4-sulfamoylphenethyl)-piperidin-4-yl]-6-methoxyindoline



1-(Piperidin-4-yl)-6-methoxyindoline (350 mg) and 4-sulfamoylphenethyl bromide (340 mg) were treated as in Example 2 to give the title compound (70 mg) as a brown powder (yield: 13%).

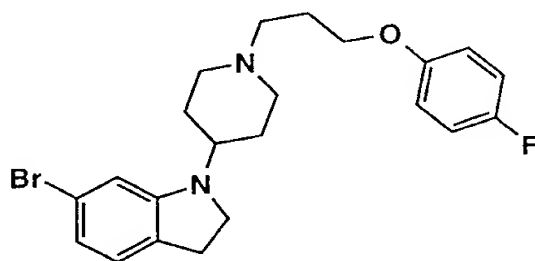
m.p.: 179 - 182°C.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.71-1.90 (4H, m), 2.11-2.29 (2H, m), 2.61-2.70 (2H,

m), 2.82-2.98 (4H, m), 3.10-3.21 (2H, m), 3.31-3.41 (3H, m), 3.78 (3H, s), 4.98 (2H, br-s), 6.00 (1H, s), 6.12 (1H, d, J=8Hz), 6.94 (1H, d, J=8Hz), 7.35 (1H, d, J=8Hz), 7.85 (1H, d, J=8Hz). FAB-Mass: 416 (MH+).

Example 231: Synthesis of 1-[1-(4-fluorophenoxypropyl)-piperidin-4-yl]-6-bromoindoline

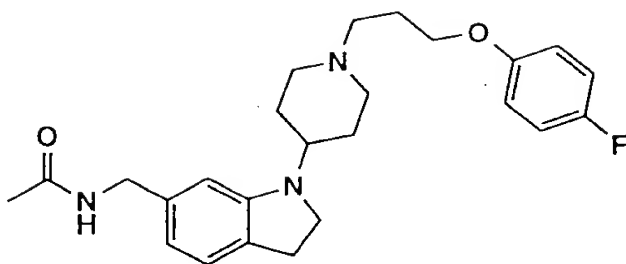


1-(Piperidin-4-yl)-6-bromoindoline (1.6 g) and 4-fluorophenoxypropyl bromide (1.6 g) were treated as in Example 2 to give the title compound (2.2 g) as a white powder (yield: 90%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.51-1.85 (2H, m), 1.87-1.89 (2H, m), 1.92-2.19 (4H, m), 2.52-2.62 (2H, m), 2.90 (2H, t, J=8Hz), 3.03-3.14 (2H, m), 3.28-3.33 (1H, m), 3.42 (2H, t, J=8Hz), 3.97 (2H, t, J=6Hz), 6.45 (1H, s), 6.68 (1H, d, J=8Hz), 6.80-6.89 (3H, m), 6.92-7.00 (2H, m).

Example 232: Synthesis of 1-[1-(4-fluorophenoxypropyl)-piperidin-4-yl]-6-acetamidomethylindoline



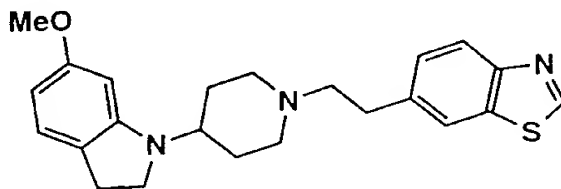
1-[1-(4-Fluorophenoxypropyl)piperidin-4-yl]-6-bromoindoline (1.2 g) was treated as in Examples 130, 131 and 133 to give the oxalate (46 mg) of the title compound as a brown hygroscopic amorphous solid (yield: 3.2%).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.77-1.93(4H, m), 2.03-2.13(2H, m), 2.08(3H, s), 2.84(2H, t, J=8Hz), 2.85-2.99(2H, m), 3.04-3.12(2H, m), 3.31(2H, t, J=8Hz), 3.44-3.53(2H, m), 3.60-3.69(1H, m), 4.03(2H, t, J=6Hz), 4.13(2H, d, J=6Hz), 6.39(1H, s), 6.45(1H, d, J=8Hz), 6.93-6.98(3H, m), 7.11-7.16(2H, m), 8.21(1H, t, J=6Hz).

FAB-Mass: 426(MH⁺).

Example 233: Synthesis of 1-[1-[2-(6-benzothiazolylethyl)-piperidin-4-yl]-6-methoxyindoline



6-(2-Bromoethyl)benzothiazole (0.108 g) and 1-(piperidin-4-yl)-6-methoxyindoline (0.105 g) were treated as

in Example 2 to give the title compound (0.145 g) as a yellow oil (yield: 81.9%).

Next, oxalic acid (37 mg) was added thereto to give a salt followed by recrystallization from ethanol. Thus the oxalate (0.097 g) of the title compound was obtained.

m.p.: 188°C.

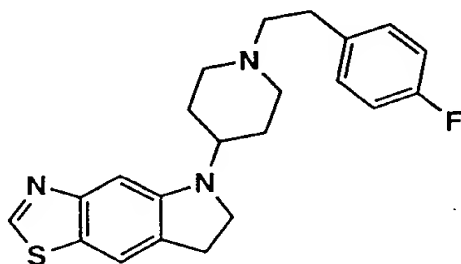
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.87(4H, m), 2.82(2H, t, J=7.6Hz), 3.21(2H, br-t), 3.18(2H, m), 3.28(2H, m), 3.34(2H, t, J=7.6Hz), 3.58(2H, m), 3.70(3H, s), 3.72(1H, m), 6.12(1H, d, J=7.6Hz), 6.15(1H, s), 6.91(1H, d, J=7.6Hz), 7.50(1H, d, J=8.4Hz), 8.08(1H, d, J=8.4Hz), 8.10(1H, s), 9.39(1H, s).

ESI-Mass: 394.2 (MH⁺).

Example 234: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]thiazolo[5,4-f]indoline



Thiazolo[5,4-f]indoline (0.2 g), 1-(4-fluorophenethyl)-4-piperidone (0.6 g), acetic acid (0.66 g) and triacetoxylated sodium borohydride (0.79 g) were treated as in

Example 101 to give the hydrochloride (0.34 g) of the title compound as a yellow powder (yield: 71%).

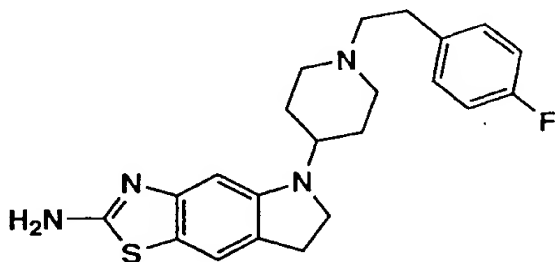
m.p. (hydrochloride): 165°C (decomp.).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.93-2.06 (4H, m), 2.98-3.06 (4H, m), 3.08-3.19 (2H, m), 3.24-3.32 (2H, m), 3.43 (2H, t, J=8Hz), 3.60-3.70 (2H, m), 3.81-3.90 (1H, m), 7.16-7.20 (3H, m), 7.31-7.36 (2H, m), 7.70 (1H, s), 9.14 (1H, s).

FAB-Mass: 382 (MH⁺)

Example 235: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-aminothiazolo[5,4-f]indoline



Bromine (0.22 ml) was added dropwise into a solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminoindoline (1.2 g) and potassium thiocyanate (1.0 g) in acetic acid (12 ml) and the resultant mixture was heated at 100°C for 1 hr. Under ice cooling, a 5 N aqueous solution of sodium hydroxide and chloroform were added to the reaction solution and the layers were separated. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. Then the residue was

purified by silica gel column chromatography (methylene chloride/ethanol system) to give the title compound (0.20 g) as a brown powder (yield: 14%).

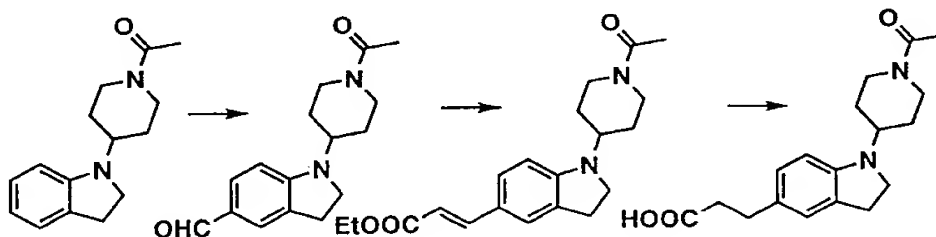
m.p.: 173°C (decomp.).

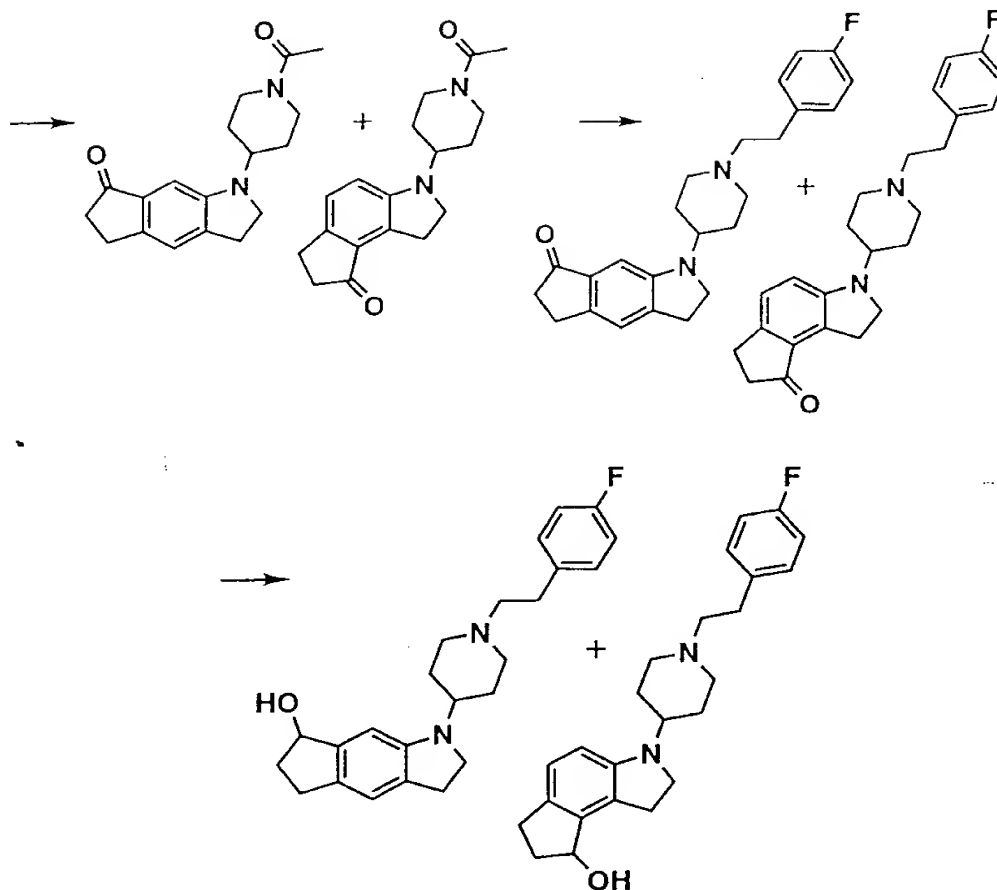
¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.68-1.90 (2H, m), 2.07-2.16 (2H, m), 2.55-2.61 (2H, m), 2.75-2.82 (2H, m), 2.97 (2H, t, J=8Hz), 3.07-3.14 (2H, m), 3.36-3.45 (1H, m), 3.41 (2H, t, J=8Hz), 5.25 (2H, br-s), 6.62 (1H, s), 6.94-6.99 (2H, m), 7.14-7.19 (3H, m).

FAB-Mass: 397 (MH⁺).

Example 236: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-7-hydroxy-(4a,7a)-cyclohexanoindoline and 1-[1-(4-fluorophenethyl)piperidin-4-yl]-4-hydroxy-(3b,6a)-cyclohexanoindoline and oxalates thereof





Under ice cooling, triethyl phosphonoacetate (2.24 g) was added dropwise into a suspension of 60% sodium hydride (0.4 g) in THF (30 ml). After the completion of the evolution of hydrogen, a solution of 1-(1-acetylpiperidin-4-yl)-indoline-7-carboxaldehyde (2.4 g) in THF (20 ml) was added dropwise into the reaction solution and the resultant mixture was reacted at room temperature for 3 hr. Then the reaction solution was partitioned between ethyl acetate and water followed by washing with water, drying and concentration under reduced pressure.

The resulting residue was dissolved in ethanol (50 ml). After adding 10% palladium carbon (0.3 g) thereto, hydrogenation was carried out under atmospheric pressure. After the completion of the reaction, the reaction solution was filtered through celite and washed with ethanol. A 5 N aqueous solution (5 ml) of sodium hydroxide was added to the filtrate and the resultant mixture was reacted at 50°C for 1 hr. After cooling the reaction solution, a 5 N aqueous solution (5 ml) of hydrochloric acid was added thereto followed by concentration under reduced pressure. Then methylene chloride (100 ml) was added to the residue and the resultant mixture was filtered through celite. The filtrate was concentrated.

To the resulting crude carboxylic acid (1.8 g) thus obtained was added polyphosphoric acid (30 g) and the resultant mixture was reacted at 120°C for 2 hr. Next, the reaction solution was cooled to 50°C and water (200 ml) was added thereto followed by extraction with ethyl acetate. The ethyl acetate layer was washed successively with water, a 10% aqueous solution of potassium carbonate, water and brine, dried and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane system) to give a mixture (0.31 g) of cyclopentanone derivatives as a colorless oil.

This mixture was dissolved in ethanol (15 ml). After

adding an 8 N aqueous solution (5 ml) of sodium hydroxide thereto, the resultant mixture was heated under reflux for 6 hr. Then the reaction solution was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and an aqueous solution of ammonium chloride. The ethyl acetate layer was washed with water, dried and concentrated under reduced pressure. The resulting residue was purified by silica gel short column chromatography (methylene chloride/methanol system) to give a pale brown oil (0.21 g).

This oily mixture (0.20 g), 4-fluorophenethyl bromide (0.18 g) and potassium carbonate (0.43 g) were suspended in DMF (15 ml) and then reacted at 60°C for 12 hr. The reaction solution was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with water and brine, dried and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system) to give a mixture (0.12 g) of ketone derivatives as a colorless oil.

This mixture was dissolved in methanol and sodium borohydride was added thereto at room temperature. After reacting for 30 min, the solvent was evaporated under reduced pressure. Then the residue was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with water, dried and concentrated under reduced pressure. The

resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system) to give 1-[1-(4-fluorophenethyl)piperidin-4-yl]-7-hydroxy-(4a,7a)-cyclohexanoindoline (0.04 g) and 1-[1-(4-fluorophenethyl)-piperidin-4-yl]-4-hydroxy-(3b,6a)-cyclohexanoindoline (0.03 g) each as a colorless oil. These compounds were each dissolved in methanol and reacted with oxalic acid. After removing the solvent, ether was added to the residue. The resulting precipitate was collected by filtration and dried. Thus the oxalates of the title compounds were obtained each as an amorphous solid.

(1) 1-[1-(4-Fluorophenethyl)piperidin-4-yl]-7-hydroxy-(4a,7a)-cyclohexanoindoline

Oxalate

¹H-NMR (400 MHz, CD₃OD):

δ(ppm) 1.87 (1H, m), 2.04 (4H, m), 2.39 (1H, m), 2.63 (1H, m), 2.86 (3H, m), 3.02-3.25 (4H, m), 3.30-3.40 (4H, m), 3.70-3.85 (3H, m), 5.06 (1H, br-t), 6.56 (1H, s), 6.92 (1H, s), 7.05 (2H, t, J=8.0Hz), 7.31 (2H, br).

FAB-Mass: 381 (MH⁺).

(2) 1-[1-(4-Fluorophenethyl)piperidin-4-yl]-4-hydroxy-(3b,6a)-cyclohexanoindoline

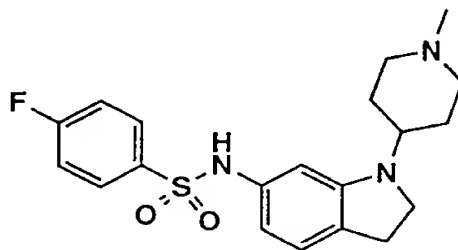
Oxalate

¹H-NMR (400 MHz, CD₃OD):

δ (ppm) 1.87-2.06 (5H, m), 2.37 (1H, m), 2.65 (1H, m), 2.93 (2H, m), 3.02-3.23 (5H, m), 3.30-3.40 (4H, m), 3.70-3.84 (3H, m), 5.15 (1H, br-t), 6.48 (1H, d, J=8.0Hz), 6.92 (1H, d, J=8.0Hz), 7.05 (2H, t, J=8.0Hz), 7.32 (2H, br-t).

FAB-Mass: 381 (MH+).

Example 237: Synthesis of 1-(1-methylpiperidin-4-yl)-6-(4-fluorobenzenesulfonylamino)indoline



6-(4-Fluorobenzenesulfonylamino)indoline (0.3 g), 1-methyl-4-piperidone (0.17 g), acetic acid (0.36 g) and triacetoxylated sodium borohydride (0.41 g) were treated as in Example 101 to give the hydrochloride (0.08 g) of the title compound as a pale yellow powder (yield: 19%).

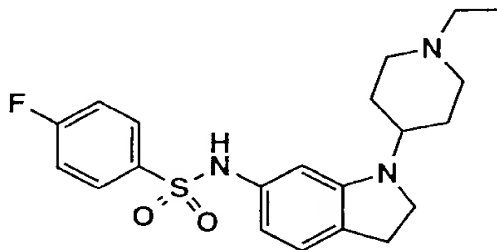
m.p. (hydrochloride): 170 - 172°C.

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6):

δ (ppm) 1.63-1.71 (2H, m), 1.80-1.94 (2H, m), 2.71 (3H, s), 2.76 (2H, t, J=8Hz), 3.03-3.14 (2H, m), 3.24 (2H, t, J=8Hz), 3.40-3.56 (3H, m), 6.18 (1H, d, J=8Hz), 6.22 (1H, s), 6.81 (1H, d, J=8Hz), 7.35-7.39 (2H, m), 7.69-7.78 (2H, m).

FAB-Mass: 390 (MH+).

Example 238: Synthesis of 1-(1-ethylpiperidin-4-yl)-6-(4-fluorobenzenesulfonylamino)indoline



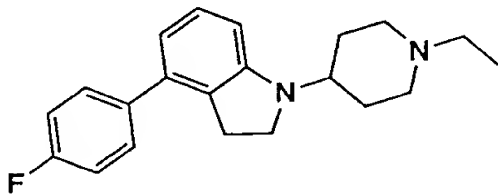
6-(4-Fluorobenzenesulfonylamino)indoline (0.3 g), 1-ethyl-4-piperidone (0.19 g), acetic acid (0.36 g) and triacetoxylated sodium borohydride (0.41 g) were treated as in Example 101 to give the hydrochloride (0.34 g) of the title compound as a pale yellow hygroscopic amorphous solid (yield: 77%).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.22 (3H, t, J=7Hz), 1.62-1.71 (2H, m), 1.80-1.99 (2H, m), 2.76 (2H, t, J=8Hz), 2.95-3.19 (4H, m), 3.22 (2H, t, J=8Hz), 3.48-3.80 (3H, m), 6.16 (1H, d, J=8Hz), 6.23 (1H, s), 6.81 (1H, d, J=8Hz), 7.31-7.40 (2H, m), 7.70-7.80 (2H, m).

FAB-Mass: 390 (MH⁺).

Example 239: Synthesis of 1-(1-ethylpiperidinyl)-4-(4-fluorophenyl)indoline



4-(4-Fluorophenyl)indoline (250 mg), 1-ethyl-4-piperidone (230 mg), acetic acid (430 mg) and triacetoxylated sodium borohydride (510 mg) were treated as in Example 1 to give the hydrochloride (200 mg) of the title compound as a white powder (yield: 46%).

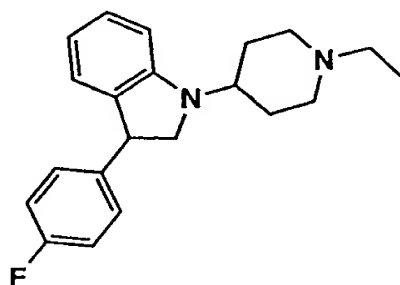
m.p. (hydrochloride): 270°C (decomp.).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.23 (3H, t, J=7Hz), 1.83-2.04 (4H, m), 2.91-3.12 (6H, m), 3.24-3.34 (2H, m), 3.50-3.57 (2H, m), 3.70-3.80 (1H, m), 6.54 (1H, d, J=8Hz), 6.60 (1H, d, J=8Hz), 7.09 (1H, t, J=8Hz), 7.21-7.26 (2H, m), 7.45-7.48 (2H, m), 9.89 (1H, br-s).

FAB-Mass: 325 (MH⁺).

Example 240: Synthesis of 1-(1-ethylpiperidin-4-yl)-3-(4-fluorophenyl)indoline



3-(4-Fluorophenyl)indoline (0.184 g) was treated as in Example 16 to give the title compound (0.102 g) as a yellow oil (yield: 38.0%).

Next, oxalic acid (14 mg) was added thereto to give a salt followed by recrystallization from ethanol. Thus the oxalate

(0.063 g) of the title compound was obtained.

m.p. (oxalate): 216°C.

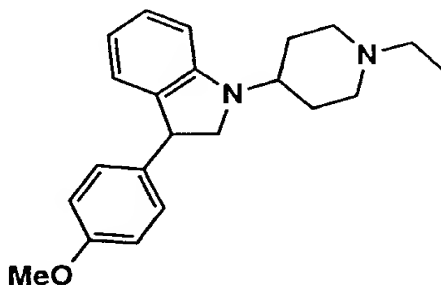
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.20(3H, t, J=6.8Hz), 1.90(4H, m), 2.96(2H, m), 3.04(2H, m), 3.23(1H, t, J=8.2Hz), 3.48(2H, m), 3.75(2H, m), 4.42(1H, t, J=8.2Hz), 6.58(1H, t, J=7.6Hz), 6.64(1H, d, J=7.6Hz), 6.78(1H, d, J=7.6Hz), 7.06(1H, t, J=7.6Hz), 7.14(2H, t, J=8.4Hz), 7.28(1H, dd, J=5.6, 8.4Hz).

FAB-Mass: 325(MH+).

Example 241: Synthesis of 1-(1-ethylpiperidin-4-yl)-3-(4-methoxyphenyl)indoline



Methoxymethyltriphenylphosphonium bromide (7.113 g) and 4-anisaldehyde (2.6 ml) were treated as in Production Example 41-1 to give a pale yellow, oil (2.235 g). Then this product was dissolved in isopropanol (25 ml) and 2 N hydrochloric acid (25 ml). After adding phenylhydrazine (1.0 ml), the resultant mixture was heated under reflux for 1 hr. Then the reaction solution was allowed to cool and concentrated under reduced

pressure. Next, ethyl acetate was added thereto and the layers were separated. The organic layer was washed with saturated aqueous solution of sodium bicarbonate and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give a yellow oil (1.249 g). The resulting product was treated as in Production Example 54 to give a yellow oil (0.534 g).

Subsequently, this product and 1-ethyl-4-piperidone were treated as in Example 16 to give the title compound (0.307 g) as a yellow oil (yield: 4.4%).

Next, oxalic acid (41 mg) was added thereto to give a salt followed by recrystallization from ethanol. Thus the oxalate (0.151 g) of the title compound was obtained as pale yellow crystals.

m.p. (oxalate): 143°C.

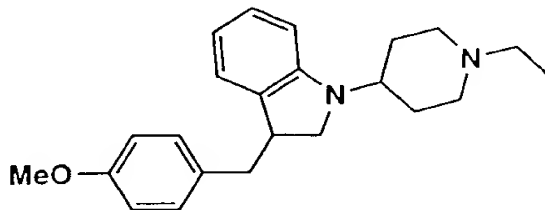
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.20(3H, t, J=7.2Hz), 1.89(4H, m), 2.95(2H, m), 3.04(2H, m), 3.19(1H, t, J=8.4Hz), 3.48(2H, m), 3.72(3H, s), 3.75(2H, m), 4.34(1H, t, J=8.4Hz), 6.57(1H, t, J=7.6Hz), 6.62(1H, d, J=7.6Hz), 6.75(1H, d, J=7.6Hz), 6.88(2H, d, J=8.8Hz), 7.05(1H, t, J=7.6Hz), 7.16(2H, t, J=8.8Hz).

ESI-Mass: 337.1(MH+).

Example 242: Synthesis of 1-(1-ethylpiperidin-4-yl)-3-(4-methoxybenzyl)indoline



3-(4-Methoxybenzyl)indoline (0.332 g) and 1-ethyl-4-piperidone (0.28 ml) were treated as in Example 16 to give the title compound (0.380 g) as a pale yellow oil (yield: 78.0%).

Next, oxalic acid (49 mg) was added thereto to give a salt followed by recrystallization from acetone. Thus the oxalate (0.150 g) of the title compound was obtained.

m.p. (oxalate): 136°C.

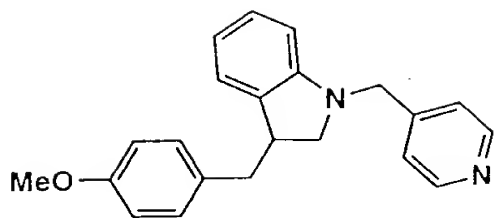
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.18(3H, t, J=7.6Hz), 1.80(4H, m), 2.63(1H, dd, J=9.2, 13.6Hz), 2.89(2H, m), 2.99(4H, m), 3.23(1H, t, J=8.6Hz), 3.44(3H, m), 3.67(1H, m), 3.73(3H, s), 6.51(1H, d, J=7.6Hz), 6.55(1H, t, J=7.6Hz), 6.87(2H, d, J=8.4Hz), 6.92(1H, d, J=7.6Hz), 7.01(1H, t, J=7.6Hz), 7.15(2H, d, J=8.4Hz).

ESI-Mass: 351.3(MH⁺).

Example 243-1: Synthesis of 1-(4-pyridylmethyl)-3-(4-methoxybenzyl)indoline

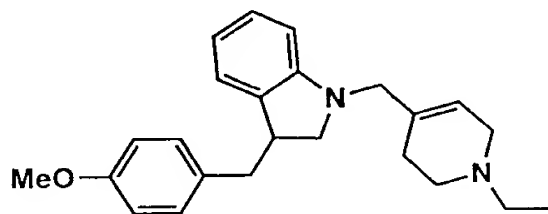


3-(4-Methoxybenzyl)indoline (2.0 g) and 4-pyridinecarboxyaldehyde (1.2 ml) were treated as in Example 16 to give the title compound (1.474 g) as a pale yellow oil (yield: 53.44%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 2.27(1H, d, J=8.8, 14.0Hz), 3.08(2H, m), 3.36(1H, t, J=8.8Hz), 3.55(1H, m), 3.79(3H, s), 4.20(2H, d, J=7.6Hz), 7.00(1H, d, J=7.6Hz), 7.06(3H, m), 7.20(2H, m), 8.53(2H, dd, J=1.6, 4.8Hz).

Example 243-2: Synthesis of 1-[(1-ethylpiperidin-3-en-4-yl)methyl]-3-(4-methoxybenzyl)indoline



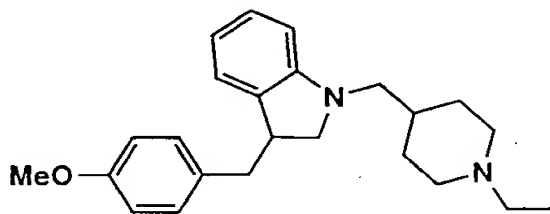
1-(4-Pyridylmethyl)-3-(4-methoxybenzyl)indoline (0.7 g) was dissolved in acetonitrile (10 ml). After adding ethyl iodide (0.29 ml), the mixture was heated in a sealed tube at 70 to 90°C for 9 hr. After allowing to cool, the reaction solution was concentrated under reduced pressure. Then

ethanol (20 ml) and sodium borohydride (0.40 g) were added to the residue followed by stirring at room temperature for 1 hr. The reaction solution was concentrated under reduced pressure, diluted with ethyl acetate (200 ml), washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (0.115 g) as a pale yellow oil (yield: 15.0%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.12(3H, t, J=7.2Hz), 2.14(2H, m), 2.48(2H, q, J=7.2Hz), 2.56(2H, m), 2.73(1H, dd, J=9.2, 14.4Hz), 2.96(2H, br-d), 3.01(2H, m), 3.40(2H, t, J=9.2Hz), 3.53(2H, br-s), 3.79(3H, s), 5.58(1H, br-s), 6.47(1H, d, J=9.1Hz), 6.61(1H, d, J=9.1Hz), 6.83(2H, m), 6.83(2H, m), 6.91(1H, d, J=8.0Hz), 6.47(1H, d, J=9.1Hz), 7.07(3H, m).

Example 243-3: Synthesis of 1-[(1-ethylpiperidin-4-yl)methyl]-3-(4-methoxybenzyl)indoline



1-[(1-Ethylpiperidin-3-en-4-yl)methyl]-3-(4-methoxybenzyl)indoline (0.115 g) was dissolved in ethanol (3.2 ml). After adding a palladium carbon catalyst thereto,

catalytic reduction was carried out under atmospheric pressure at room temperature for 54 hr. Then the catalyst was filtered off and the filtrate was concentrated under reduced pressure. The resulting residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (0.053 g) as a pale yellow oil (yield: 45.8%).

Next, oxalic acid (6 mg) was added thereto to give a salt followed by recrystallization from a solvent mixture of ethyl acetate with isopropyl ether. Thus the oxalate (0.313 g) of the title compound was obtained as colorless crystals.

m.p. (oxalate): 78°C.

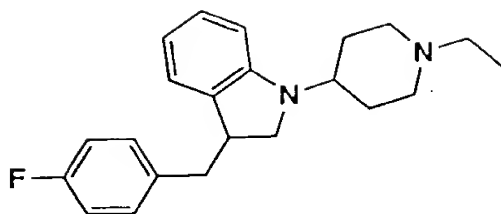
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.17(3H, t, J=7.2Hz), 1.38(2H, m), 1.82(2H, br-t), 2.64(1H, dd, J=8.6, 14.0Hz), 2.75(2H, br-t), 2.83(1H, m), 2.97(4H, m), 3.29(1H, t, J=8.6Hz), 3.34(2H, br-d), 3.45(1H, m), 3.73(3H, s), 6.48(1H, d, J=7.6Hz), 6.55(1H, t, J=7.6Hz), 6.86(2H, d, J=8.4Hz), 6.94(1H, d, J=7.6Hz), 6.99(1H, t, J=7.6Hz), 7.14(2H, d, J=8.4Hz).

FAB-Mass: 365(MH+).

Example 244: Synthesis of 1-(1-ethylpiperidin-4-yl)-3-(4-fluorobenzyl)indoline



3-(4-Fluorobenzyl)indoline (1.163 g) and 1-ethyl-4-piperidone (1.0 ml) were treated as in Example 16 to give the title compound (1.614 g) as a yellow oil (yield: 93.7%).

Next, oxalic acid (21 mg) was added thereto to give a salt followed by recrystallization from ethanol. Thus the oxalate of the title compound was obtained.

m.p. (oxalate): 203°C.

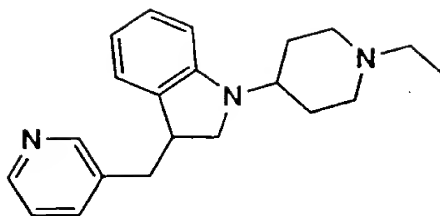
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.20(3H, t, J=7.2Hz), 1.82(4H, m), 2.70(1H, dd, J=8.8, 13.2Hz), 2.90-3.07(6H, m), 3.26(1H, t, J=8.8Hz), 3.41-3.50(3H, m), 3.68(1H, m), 6.54(2H, m), 6.91(1H, d, J=7.6Hz), 7.02(1H, t, J=7.6Hz), 7.12(2H, t, J=8.8Hz), 7.27(1H, dd, J=5.6, 8.8Hz).

ESI-Mass: 339.2(MH+).

Example 245: Synthesis of 1-(1-ethylpiperidin-4-yl)-3-(3-pyridylmethyl)indoline



3-(3-Pyridylmethyl)indoline (0.253 g) was treated as in Example 16 to give the title compound (0.233 g) as a yellow oil (yield: 71.0%).

Next, oxalic acid (65 mg) was added thereto to give a salt followed by recrystallization from ethanol. Thus the oxalate (0.191 g) of the title compound was obtained (yield: 45.5%).
m.p. (oxalate): 149°C.

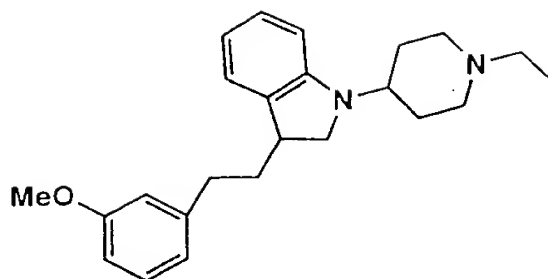
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.20(3H, t, J=7.6Hz), 1.83(4H, m), 2.76(1H, dd, J=8.8, 11.6Hz), 3.04(6H, m), 3.29(1H, t, J=8.8Hz), 3.50(3H, m), 3.68(1H, m), 6.52(1H, d, J=7.6Hz), 6.56(1H, t, J=7.6Hz), 6.92(1H, d, J=7.6Hz), 7.02(1H, t, J=7.6Hz), 7.32(1H, dd, J=4.8, 8.0Hz), 7.65(1H, dt, J=2.0, 8.0Hz), 8.43(2H, m).

ESI-Mass: 322.2(MH⁺).

Example 246: Synthesis of 1-(1-ethylpiperidin-4-yl)-3-(3-methoxyphenethyl)indoline



3-(3-Methoxyphenethyl)indoline (0.133 g) was treated as in Example 16 to give the title compound (0.132 g) as a yellow oil (yield: 52.3%).

Next, hydrochloric acid was added thereto to give the hydrochloride of the title compound as a hygroscopic amorphous solid.

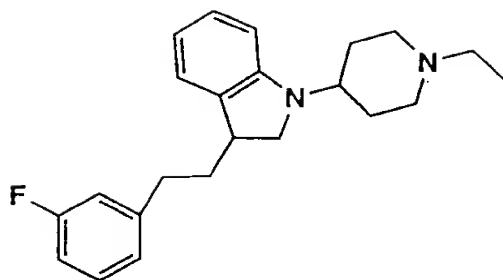
Hydrochloride

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO}-d_6$):

δ (ppm) 1.26(3H, t, $J=8.0\text{Hz}$), 1.74(1H, m), 1.86(2H, m), 2.07(3H, m), 2.63(2H, t, $J=8.0\text{Hz}$), 2.99-3.07(5H, m), 3.14(1H, m), 3.52(3H, t, $J=8.0\text{Hz}$), 3.72(1H, m), 3.74(3H, s), 6.59(2H, m), 7.02(1H, t, $J=8.0\text{Hz}$), 7.08(1H, d, $J=8.0\text{Hz}$), 7.20(1H, d, $J=8.0\text{Hz}$).

ESI-Mass: 365.2(MH+).

Example 247: Synthesis of 1-(1-ethylpiperidin-4-yl)-3-(3-fluorophenethyl)indoline



3-(3-Fluorophenethyl)indoline (0.582 g) was treated as in Example 16 to give the title compound (0.641 g) as a yellow oil (yield: 66.2%).

Next, oxalic acid (68 mg) was added thereto to give a salt followed by recrystallization from ethyl acetate. Thus the oxalate (0.313 g) of the title compound was obtained as colorless crystals.

m.p. (oxalate): 138°C.

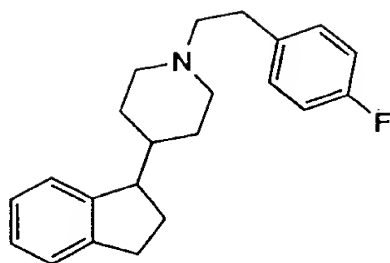
Oxalate

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.22(3H, t, J=7.2Hz), 1.72(1H, m), 1.89(4H, m), 2.07(1H, m), 2.67(2H, t, J=8.4Hz), 2.97(2H, br-t), 3.12(1H, m), 3.50(3H, t, J=8.4Hz), 3.70(1H, m), 6.53(1H, d, J=7.6Hz), 6.58(1H, d, J=7.6Hz), 7.00(2H, m), 7.06(1H, d, J=7.6Hz), 7.09(2H, m), 7.32(1H, q, J=7.6Hz).

ESI-Mass: 353.1(MH⁺).

Example 248: Synthesis of 1-[1-(4-fluorophenethyl)-piperidin-4-yl]indan



1-(Piperidin-4-yl)indan (300 mg) and 4-fluorophenethyl bromide (370 mg) were treated as in Example 2 to give the hydrochloride (250 mg) of the title compound as a white powder (yield: 46%).

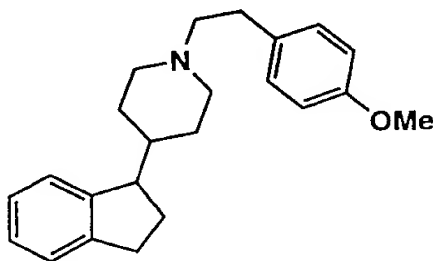
m.p. (hydrochloride): 222 - 224°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.50-1.98(6H, m), 2.01-2.12(1H, m), 2.72-2.94(4H, m), 2.98-3.04(2H, m), 3.08-3.22(3H, m), 3.46-3.57(2H, m), 7.11-7.22(6H, m), 7.28-7.31(2H, m), 10.33(1H, br-s).

FAB-Mass: 324(MH⁺).

Example 249: Synthesis of 1-[1-(4-methoxyphenethyl)-piperidin-4-yl]indan



1-(Piperidin-4-yl)indan (300 mg) and 4-methoxyphenethyl bromide (390 mg) were treated as in Example 2 to give the hydrochloride (260 mg) of the title compound as a white powder

(yield: 47%).

m.p. (hydrochloride): 191°C (decomp.).

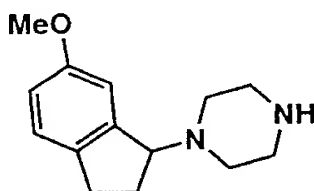
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.48-1.57(1H, m), 1.60-1.97(5H, m), 2.01-2.11(1H, m), 2.71-3.00(6H, m), 3.08-3.18(3H, m), 3.45-3.56(2H, m), 3.70(3H, s), 6.87(2H, d, J=8Hz), 7.11-7.23(6H, m), 10.43(1H, br-s).

FAB-Mass: 336(MH+).

Example 250: Synthesis of 1-{4-[2-(4-fluorophenyl)ethyl]-piperazin-1-yl}-6-methoxyindan hydrochloride

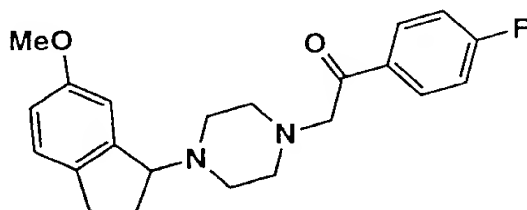
(250-1) 1-(Piperazin-1-yl)-6-methoxyindan



1-(4-Acetylpiperazin-1-yl)-6-methoxyindan (2.20 g)

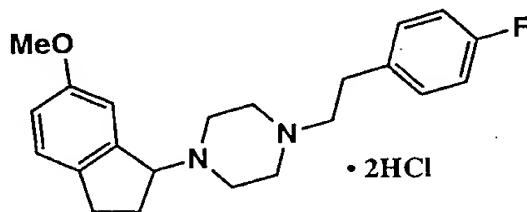
obtained as an intermediate in the above Example and an 8 N aqueous solution (8.0 ml) of sodium hydroxide were heated under reflux in ethanol. Then the reaction mixture was concentrated under reduced pressure, extracted with methylene chloride, dried and concentrated under reduced pressure again. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system) to give the title compound (1.48 g) as a wax (yield: 73%).

(250-2) 1-[4-(4-Fluorophenacyl)piperazin-1-yl]-6-methoxyindan



In the presence of a 5 N aqueous solution (2.0 ml) of sodium hydroxide, 1-(piperazin-1-yl)-6-methoxyindan (0.41 g) and 4-fluorophenacyl chloride (0.46 g) were reacted in methylene chloride at 0°C. Then, the reaction mixture was extracted with methylene chloride. The methylene chloride layer was washed with water, dried and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (toluene/acetone system) to give the title compound (0.60 g).

(250-3) 1-[4-[2-(4-Fluorophenyl)ethyl]piperazin-1-yl]-6-methoxyindan hydrochloride



Lithium aluminum hydride (0.13 g) was suspended in THF. Into the resultant suspension was added dropwise a solution of 1-[4-(4-fluorophenacyl)piperazin-1-yl]-6-methoxyindan (0.60

g) in THF and the reaction mixture was heated under reflux while monitoring the reaction by TLC. Then the reaction solution was ice cooled and water (0.13 ml), a 5 N aqueous solution (0.13 ml) of sodium hydroxide and water (0.39 ml) were successively added thereto followed by stirring at room temperature for 1 hr. The resulting precipitate was filtered off and washed with THF. The filtrate was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system) to give an oil (0.48 g) (yield: 83%).

This oily product was converted into a hydrochloride in a conventional manner to give the title compound as a white powder.

m.p.: 213°C (decomp.).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 2.03-2.19(2H, m), 2.49-2.66(10H, m), 2.69-2.90(4H, m), 3.80(3H, s), 4.32(1H, t, J=7.2Hz), 6.77(1H, dd, J=8.4, 2.8Hz), 6.90(1H, d, J=2.8Hz), 6.93-6.99(2H, m), 7.11(1H, d, J=8.4Hz), 7.12-7.17(2H, m).

FAB-Mass: 355(MH+).

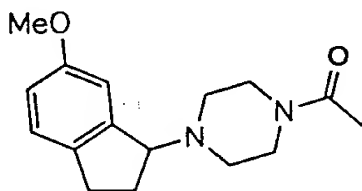
Example 251: Synthesis of 1-(4-ethylpiperazin-1-yl)-6-methoxyindan hydrochloride

(251-1) 1-Chloro-6-methoxyindan



6-Methoxyindan-1-one (5.0 g) was dissolved in methanol (50 ml). Next, sodium tetrahydroborate (1.41 g) was added thereto at 0°C, and the resultant mixture was reacted at room temperature for 5 hr. The reaction solution was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with water, dried and concentrated under reduced pressure to give 6-methoxyindan-1-ol (5.1 g) as an oil. This alcohol was not purified but reacted as such with thionyl chloride (4.5 ml) in ether at room temperature for 6 hr. The reaction solution was poured into ice water and extracted with ether. The ether layer was washed with water, dried and concentrated under reduced pressure to give the title compound (2.76 g).

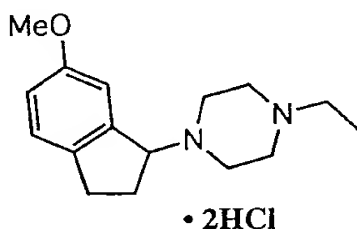
(251-2) 1-(4-Acetylpiperazin-1-yl)-6-methoxyindan



1-Chloro-6-methoxyindan (2.76 g), 1-acetylpiperazine (2.30 g) and potassium carbonate (2.90 g) were heated under

reflux in acetone overnight. Then the reaction solution was cooled, filtered and washed with acetone. The filtrate was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with water, dried and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (toluene/acetone system) to give the title compound (2.70 g) as an oil.

(251-3) 1-(4-Ethylpiperazin-1-yl)-6-methoxyindan
hydrochloride



Lithium aluminum hydride (0.14 g) was suspended in THF. Into the resultant suspension was added dropwise a solution of 1-(4-acetylpiperazin-1-yl)-6-methoxyindan (0.50 g) in THF and the reaction mixture was heated under reflux while monitoring the reaction by TLC. Then the reaction solution was ice cooled and water (0.14 ml), a 5 N aqueous solution (0.14 ml) of sodium hydroxide and further water (0.42 ml) were successively added thereto followed by stirring at room temperature for 1 hr. The resulting precipitate was filtered off and washed with THF. The filtrate was concentrated under reduced pressure and the

obtained residue was purified by silica gel column chromatography (methylene chloride/methanol system) to give 1-(4-ethylpiperazin-1-yl)-6-methoxyindan (0.30 g) as an oil (yield: 63%).

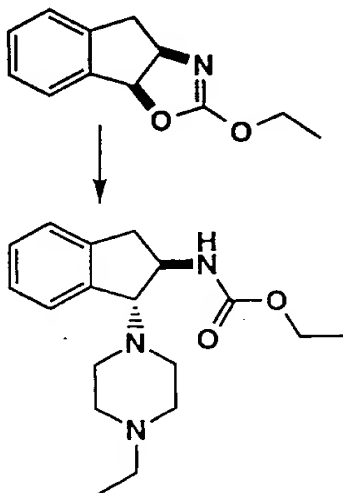
This oily product was converted into a hydrochloride in a conventional manner to give the title compound as a white powder.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.08(3H, t, J=7.2Hz), 2.02-2.19(2H, m), 2.41(2H, q, J=7.2Hz), 2.43-2.65(8H, m), 2.69-2.90(2H, m), 3.80(3H, s), 4.92(1H, t, J=7.2Hz), 6.77(1H, dd, J=8.4, 2.8Hz), 6.90(1H, d, J=2.8Hz), 7.09(1H, d, J=8.4Hz).

FAB-Mass: 261(MH⁺).

Example 252: Synthesis of trans-1-(4-ethylpiperazin-1-yl)-2-ethoxycarboxyaminoindan



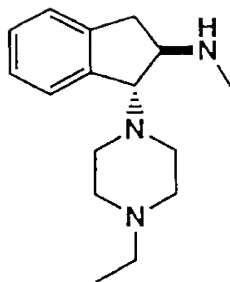
A mixture of (±)-(Z)-2-ethoxy-3a,8b-dihydro-4H-

indeno[2,1-d]oxazole (1.4 g) synthesized in accordance with the method described in WO95/04028, ethylpiperazine (1.3 ml), scandium trifluoromethanesulfonate (50 mg) and toluene (40 ml) was stirred under nitrogen atmosphere at 70°C for 17 hr as in Example 13 of WO95/04028 and Tetrahedron Lett., 1627 - 1628, 35(1994).. After allowing to cool to room temperature again, ethyl acetate and water were added to the reaction solution and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by Chromatorex NH-silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (675 mg) (yield: 31%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.07(3H, t, J=7.2Hz), 1.23(3H, m), 2.40(2H, q, J=7.2Hz), 2.45(4H, br-s), 2.68(6H, m), 3.37(1H, dd, J=16.2, 7.4Hz), 4.02(1H, d, J=4.8Hz), 4.12(2H, m), 7.16-7.23(3H, m), 7.33(1H, m).

Example 253: Synthesis of trans-1-(4-ethylpiperazin-1-yl)-2-methylaminoindan



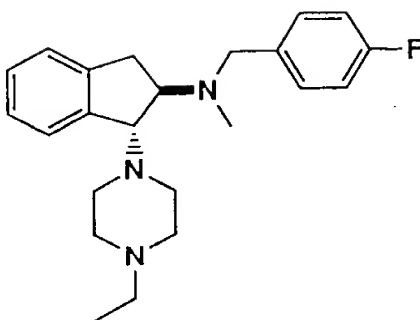
trans-1-(4-Ethylpiperazin-1-yl)-2-

ethoxycarboxyaminoindan (670 mg) was dissolved in dry ether (20 ml) and lithium aluminum hydride (401 mg) was added thereto at room temperature. Under nitrogen atmosphere, the mixture was stirred for 21 hr. Then water (0.4 ml), a 5 N aqueous solution (0.4 ml) of sodium hydroxide and further water (1.2 ml) were successively added thereto followed by stirring. The reaction solution was filtered through celite and the filtrate was concentrated under reduced pressure to give the title compound (503 mg).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.08(3H, t, J=7.2Hz), 2.42(2H, q, J=7.2Hz), 2.47(4H, m), 2.69(5H, m), 3.18(1H, dd, J=16.2, 7.4Hz), 3.48(1H, dt, J=7.4, 4.8Hz), 4.03(1H, d, J=4.8Hz), 7.14-7.21(3H, m), 7.36(1H, m).

Example 254: Synthesis of trans-1-(4-ethylpiperazin-1-yl)-2-[methyl-(4-trifluorobenzyl)aminolindan



N-Methylamine (500 mg), 4-fluorobenzaldehyde (0.52 ml), acetic acid (0.6 ml) and methylene chloride (20 ml) were treated as in Example 101 to give the title compound (670 mg) (yield: 95%).

Next, this product was dissolved in ethyl acetate (10 ml) and a solution (2 ml) of 4 N HCl in ethyl acetate was added thereto. After concentrating the solvent under reduced pressure, ether was added to the residue followed by concentration. Then, it was dried in vacuo to give the hydrochloride (821 mg) of the title compound as white crystals.

Free

$^1\text{H-NMR}$ (400 MHz, CDCl_3):

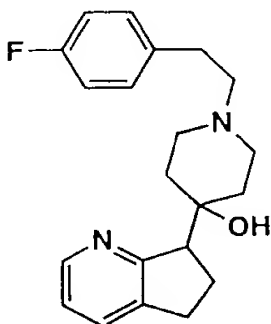
δ (ppm) 1.08(3H, t, $J=7.2\text{Hz}$), 2.10(3H, s), 2.41(2H, q, $J=7.2\text{Hz}$), 2.45(4H, br-s), 2.64(4H, br-s), 2.95(2H, m), 3.48(3H, s), 3.73(1H, ddd, $J=7.4, 7.2, 4.4\text{Hz}$), 4.33(1H, d, $J=4.4\text{Hz}$), 6.98(2H, m), 7.19(3H, m), 7.29(3H, m), 7.36(1H, m).

HCl salt

m.p.: 196 - 198°C.

FAB-Mass: 368 (MH^+).

Example 255: Synthesis of 7-[4-hydroxy-1-(4-fluorophenethyl)piperidin-4-yl]-5,6-dihydro-7H-pyridine



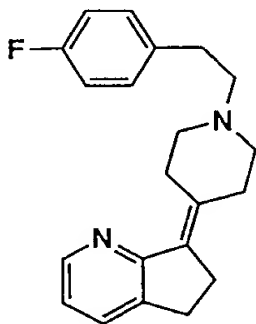
6,7-Dihydro-5H-cyclopenta[B]pyridine (1.00 g, CAS Registry No. 533-37-9) was dissolved in tetrahydrofuran (15 ml). Under a stream of nitrogen, a 1.6 M solution (5.8 ml) of n-butyllithium in hexane was added dropwise into the resultant solution while cooling to -55°C or below. After stirring for 5 min, a solution of 1-(4-fluorophenethyl)-4-piperidone (2.04 g) in tetrahydrofuran (10 ml) was added dropwise thereinto at the same temperature over 20 min. After stirring for 30 min, the reaction solution was allowed to warm to room temperature again and water was added thereto. Then it was extracted with ethyl acetate and the organic layer was washed with brine and dried over magnesium sulfate. After evaporating the solvent, the resulting residue (3.17 g) was purified by silica gel column chromatography (methanol/methylene chloride system) to give the title compound (600 mg) as a slight brown oil.

¹H-NMR (400 MHz, CDCl₃):

δ (ppm) 1.72-2.08(4H, m), 2.22-3.10(12H, m), 3.37(1H, d, $J=9.5\text{Hz}$), 5.81(1H, br-s), 6.93-7.01(2H, m), 7.08(1H, dd, $J=8.0, 5.5\text{Hz}$), 7.12-7.20(2H, m), 7.33(1H, d, $J=8.0\text{Hz}$), 8.28(1H, d, $J=5.5\text{Hz}$).

FAB-Mass: 341(MH+).

Example 256: Synthesis of 7-[1-(4-fluorophenethyl)piperidin-4-ylidene]-5,6-dihydropyrindine



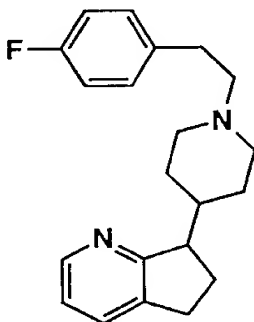
7-[4-Hydroxy-1-(4-fluorophenethyl)piperidin-4-yl]-5,6-dihydro-7H-pyrindine (350 mg) was dissolved in tetrahydrofuran (3 ml). Under ice cooling, thionyl chloride (0.11 ml) and triethylamine (0.50 ml) were added dropwise thereto. Then the resultant mixture was stirred at room temperature for 15 minutes followed by addition of water. Next, the mixture was extracted with ethyl acetate and the organic layer was washed with brine and dried over magnesium sulfate. After removing the solvent, the resulting residue (250 mg) was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (45 mg) as an oil.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 2.45-2.50(2H, m), 2.58-2.68(6H, m), 2.75-2.95(6H, m), 3.48(2H, br-s), 6.93-7.00(3H, m), 7.14-7.20(2H, m), 7.48(1H, d, J=7.6Hz), 8.40(1H, d, J=4.4Hz).

FAB-Mass: 323(MH⁺).

Example 257: Synthesis of 7-[1-(4-fluorophenethyl)piperidin-4-yl]-5,6-dihydro-7H-pyridine



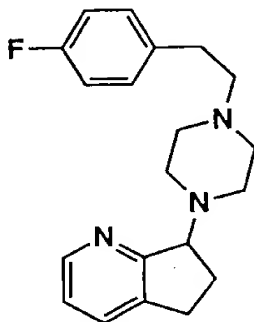
7-[1-(4-Fluorophenethyl)piperidin-4-ylidene]-5,6-dihydropyridine (100 mg) was dissolved in methanol (5 ml). After adding two drops of acetic acid thereinto, the resultant mixture was vigorously shaken in the presence of a palladium catalyst under a hydrogen gas pressure of 3 kg/cm² for 12 hr. After filtering off the catalyst, water was added to the reaction mixture followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. Then the solvent was distilled away to give the title compound (45 mg) as an oil.

¹H-NMR (400 MHz, CDCl₃):

δ (ppm) 1.22-1.52(2H, m), 1.94-2.40(4H, m), 2.55-2.96(4H, m), 3.00-3.30(6H, m), 3.45-3.70(2H, m), 6.97-7.02(2H, m), 7.07(1H, dd, $J=5.2, 7.6$ Hz), 7.19-7.25(2H, m), 7.52(1H, d, $J=7.6$ Hz), 8.34(1H, d, $J=5.2$ Hz).

FAB-Mass: 325(MH+).

Example 258: Synthesis of 7-[4-(4-fluorophenethyl)piperazin-1-yl]-5,6-dihydro-7H-pyridine



7-Hydroxy-6,7-dihydro-5H-cyclopenta[B]pyridine (247 mg) synthesized in accordance with the method described in JP-A 1-211581 was dissolved in methylene chloride (5 ml). Under ice cooling, thionyl chloride (0.147 ml) was added to the resultant solution and the resultant mixture was stirred for 25 min. Then the reaction solution was evaporated to dryness under reduced pressure. To the residue were added a solution of 1-(4-fluorophenethyl)piperazine (570 mg) synthesized in accordance with the method described in JP-A 54-92979 in dimethylformamide (5 ml) and triethylamine (0.38 ml) followed by heating at 60°C for 5 hr. After adding water, the reaction solution was

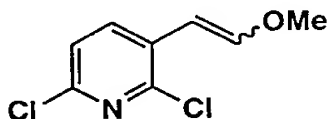
extracted with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. After evaporating the solvent, the resulting residue was purified by NH-silica gel column chromatography (hexane/methylene chloride system) to give the title compound (200 mg) as an oil.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 2.15-2.25 (2H, m), 2.50-3.00 (14H, m), 4.28 (1H, t, J=7.0Hz), 6.92-7.00 (2H, m), 7.08 (1H, dd, J=5.0, 7.4Hz), 7.12-7.18 (2H, m), 7.50 (1H, d, J=7.4Hz), 8.46 (1H, d, J=5.0Hz).

FAB-Mass: 326 (MH⁺).

Example 259-1: Synthesis of cis- and trans-2,6-dichloro-3-methoxyethylenylpyridines



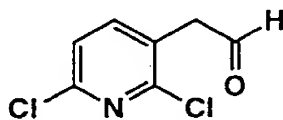
Potassium t-butoxide (22.2 g) was added to a solution of methoxymethyltriphenylphosphonium chloride (62.5 g) in tetrahydrofuran (250 ml) and the resultant mixture was stirred at 0°C for 20 min. Into the resultant solution was added dropwise a solution of 2,6-dichloro-3-formylpyridine (24.7 g) synthesized in accordance with the method described in J. CHEM. SOC. PERKIN TRANS. 1 (1990, No. 9, p. 2409.) in tetrahydrofuran (100 ml) followed by stirring for 2 hr. Then water and ethyl acetate were added to the reaction solution and the layers were

separated. The organic layer was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give a mixture (21.5 g) of the geometrical isomers of the title compound as a pale yellow oil (yield: 75%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 3.71(3H, s), 3.82(3H, s), 5.53(1H, d, J=7Hz), 5.93(1H, d, J=12Hz), 6.38(1H, d, J=7Hz), 7.03(1H, d, J=12Hz), 7.17(1H, d, J=8Hz), 7.19(1H, d, J=8Hz), 7.60(1H, d, J=8Hz), 8.36(1H, d, J=8Hz).

Example 259-2: Synthesis of 2,6-dichloro-3-formylmethypyridine



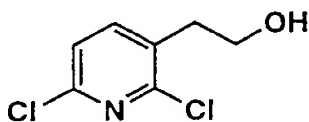
A solution of cis- and trans-2,6-dichloro-3-methoxyethylenylpyridines (21.5 g) and 35% perchloric acid (100 ml) in ether (200 ml) was stirred at room temperature for a day. Then the reaction solution was basified by adding a conc. aqueous solution of sodium hydroxide and ethyl acetate was added thereto and the layers were separated. The organic layer was washed with brine and dried over magnesium sulfate. After evaporating the solvent, the resulting residue was purified by

silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (15 g) as a pale yellow oil (yield: 56%).

$^1\text{H-NMR}$ (400 MHz, CDCl_3):

$\delta(\text{ppm})$ 3.90(2H, s), 7.31(1H, d, $J=8\text{Hz}$), 7.55(1H, d, $J=8\text{Hz}$), 9.81(1H, s).

Example 259-3: Synthesis of 2,6-dichloro-3-hydroxyethylpyridine



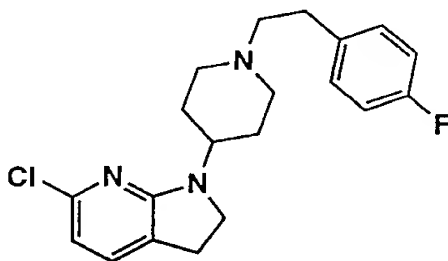
A solution of cis- and trans-2,6-dichloro-3-methoxyethylenylpyridines (2.0 g) and 35% perchloric acid (10 ml) in ether (30 ml) was stirred at room temperature for a day. Then the reaction solution was basified by adding a conc. aqueous solution of sodium hydroxide and ethyl acetate was added thereto and the layers were separated. The organic layer was washed with brine and dried over magnesium sulfate. After evaporating the solvent, ethanol (20 ml) and sodium borohydride (0.076 g) were added to the residue and the resultant mixture was stirred at room temperature for 1 hr. Then the reaction solution was concentrated under reduced pressure, diluted with a saturated aqueous solution of sodium hydrogencarbonate and ethyl acetate and the layers were separated. The organic layer

was washed with brine and dried over magnesium sulfate. After evaporating the solvent, the obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (1.3 g) as a pale yellow oil (yield: 69%).

$^1\text{H-NMR}$ (400 MHz, CDCl_3):

$\delta(\text{ppm})$ 1.50(1H, t, $J=6\text{Hz}$), 2.99(2H, t, $J=6\text{Hz}$), 3.95(1H, q, $J=6\text{Hz}$), 7.23(1H, d, $J=8\text{Hz}$), 7.62(1H, d, $J=8\text{Hz}$).

Example 259-4: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-chloro-7-azaindoline



Under ice cooling, methanesulfonyl chloride (0.45 g) was added dropwise into a solution of 2,6-dichloro-3-hydroxyethylpyridine (0.65 g) in pyridine (10 ml) and the resultant mixture was stirred for 3 hr. Then the reaction solution was concentrated under reduced pressure, diluted with a saturated aqueous solution of sodium bicarbonate and ethyl acetate and the layers were separated. The organic layer was washed with brine and dried over magnesium sulfate. After evaporating the solvent, 1-(4-fluorophenethyl)-4-

aminopiperidine (0.75 g) and dichlorobenzene (20 ml) were added to the residue and the resultant mixture was heated at 180°C for 2 hr. The reaction solution was concentrated under reduced pressure, diluted with a saturated aqueous solution of sodium bicarbonate and ethyl acetate and the layers were separated. The organic layer was washed with brine and dried over magnesium sulfate. After evaporating the solvent, the resulting residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (0.43 g) as a colorless oil (yield: 35%).

A portion of this product was converted into a hydrochloride in a conventional manner to give the title compound as a white powder.

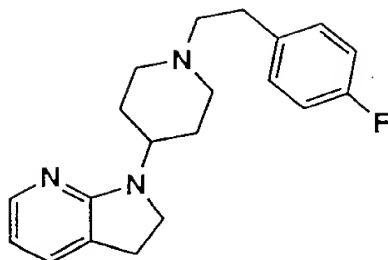
m.p. (hydrochloride): 225°C (decomp.).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.81-1.90(2H, m), 1.99-2.10(2H, m), 2.93(2H, t, J=8Hz), 3.00-3.08(2H, m), 3.10-3.27(4H, m), 3.52(2H, t, J=8Hz), 3.55-3.64(2H, m), 4.00-4.12(1H, m), 6.44(1H, d, J=8Hz), 7.12-7.20(2H, m), 7.23(1H, d, J=8Hz), 7.29-7.34(2H, m).

FAB-Mass: 360(MH+).

Example 260: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-7-azaindoline



2-Chloro-3-formylpyridine (1.5 g) synthesized in accordance with the method described in J. CHEM. SOC. PERKIN TRANS. 1 (1990, No. 9, P. 2409.) was treated as in Examples 259-1, 259-3 and 259-4 to give the hydrochloride (0.21 g) of the title compound as a white powder (yield: 4.9%).

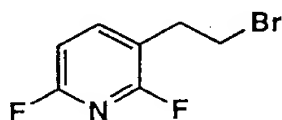
m.p. (hydrochloride): 223°C (decomp.).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.79-2.00 (2H, m), 2.03-2.21 (2H, m), 2.95-3.10 (4H, m), 3.22-3.36 (4H, m), 3.60-3.69 (4H, m), 4.15-4.24 (1H, m), 6.51-6.60 (1H, m), 7.12-7.20 (2H, m), 7.29-7.37 (3H, m), 7.67-7.73 (1H, m).

FAB-Mass: 326 (MH⁺).

Example 261-1: Synthesis of 2,6-difluoro-3-bromoethylpyridine



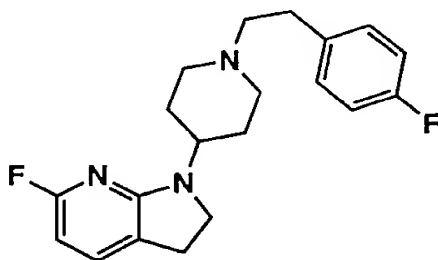
Under ice cooling, triphenylphosphine (3.1 g) and N-bromosuccinimide (1.9 g) were added to a solution of 2,6-

difluoro-3-hydroxyethylpyridine (1.58 g) obtained as in Example 259-3 in methylene chloride (100 ml) and the resultant mixture was stirred for 2 hr. After concentrating the resultant mixture under reduced pressure, the residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (1.6 g) as a colorless oil (yield: 73%).

$^1\text{H-NMR}$ (400 MHz, CDCl_3):

δ (ppm) 3.20(1H, t, $J=6\text{Hz}$), 3.59(2H, t, $J=6\text{Hz}$), 6.80-6.85(1H, m), 7.75-7.83(1H, m).

Example 261-2: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-fluoro-7-azaindoline



A mixture of 2,6-difluoro-3-bromoethylpyridine (0.3 g), 1-(4-fluorophenethyl)-4-aminopiperidine (0.3 g), triethylamine (0.27 g) and o-dichlorobenzene (20 ml) was heated at 180°C for 2 hr. Then the reaction solution was concentrated under reduced pressure, diluted with a saturated aqueous solution of sodium hydrogencarbonate and ethyl acetate and the layers were separated. The organic layer was washed with brine

and dried over magnesium sulfate. After evaporating the solvent, the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system) followed by conversion into a hydrochloride in a conventional manner to give the hydrochloride (0.14 g) of the title compound as a white powder (yield: 30%).

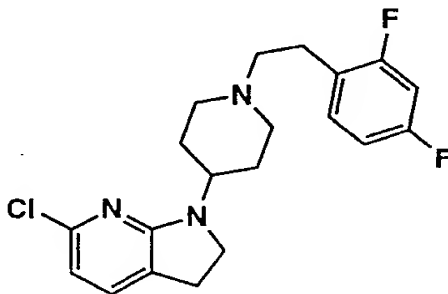
m.p. (hydrochloride): 202 - 204°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.81-1.90(2H, m), 1.99-2.11(2H, m), 2.91(2H, t, J=8Hz), 3.00-3.19(4H, m), 3.20-3.30(2H, m), 3.51(2H, t, J=8Hz), 3.58-3.65(2H, m), 3.93-4.03(1H, m), 6.03(1H, d, J=8Hz), 7.14-7.21(2H, m), 7.29-7.35(3H, m).

FAB-Mass: 344(MH⁺).

Example 262: Synthesis of 1-[1-(2,4-difluorophenethyl)-piperidin-4-yl]-6-chloro-7-azaindoline



1-(Piperidin-4-yl)-6-chloro-7-azaindoline (0.5 g) and 2,4-difluorophenethyl bromide (0.43 g) were treated as in Example 2 to give the hydrochloride (74 mg) of the title compound as a brown powder (yield: 7.8%).

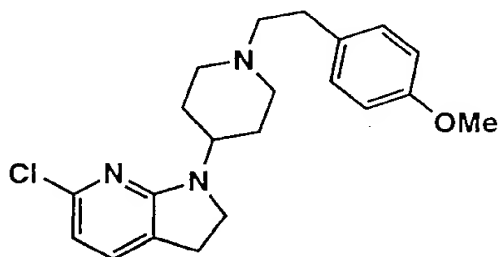
m.p. (hydrochloride): 221°C (decomp.).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.81-1.91(2H, m), 2.00-2.15(2H, m), 2.91(2H, t, J=8Hz), 3.03-3.39(6H, m), 3.53(2H, t, J=8Hz), 3.60-3.68(2H, m), 4.01-4.12(1H, m), 6.46(1H, d, J=8Hz), 7.08-7.17(1H, m), 7.21-7.31(2H, m), 7.40-7.48(1H, m).

FAB-Mass: 378(MH+).

Example 263: Synthesis of 1-[1-(4-methoxyphenethyl)piperidin-4-yl]-6-chloro-7-azaindoline



1-(Piperidin-4-yl)-6-chloro-7-azaindoline (0.8 g) and 4-methoxyphenethyl bromide (0.72 g) were treated as in Example 2 to give the hydrochloride (220 mg) of the title compound as a pale yellow powder (yield: 16%).

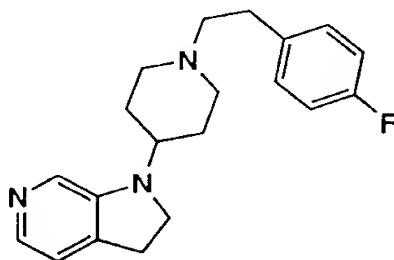
m.p. (hydrochloride): 199°C (decomp.).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.82-1.91(2H, m), 1.97-2.09(2H, m), 2.89-2.98(4H, m), 3.08-3.24(4H, m), 3.52(2H, t, J=8Hz), 3.56-3.64(2H, m), 4.00-4.10(1H, m), 6.44(1H, d, J=7Hz), 6.90(1H, d, J=9Hz), 7.18(1H, d, J=9Hz), 7.22(1H, d, J=7Hz).

FAB-Mass: 372 (MH+).

Example 264: Synthesis of 1-[1-(4-fluorophenethyl)-
piperidin-4-yl]-6-azaindoline



Under a stream of hydrogen, a mixture of 6-azaindoline (180 mg) synthesized in accordance with the method described in Tetrahedron, (1988, vol. 44, No. 10, p. 2977.), 1-(4-fluorophenethyl)-4-piperidone (530 mg), platinum oxide (20 mg), acetic acid (0.5 ml) and ethanol (10 ml) was catalytically reduced at ordinary temperature under atmospheric pressure. After stirring the reaction mixture overnight, the catalyst was filtered off and the filtrate was concentrated under reduced pressure. The resulting residue was diluted with a saturated aqueous solution of sodium hydrogencarbonate and ethyl acetate and the layers were separated. The organic layer was washed with brine and dried over anhydrous magnesium sulfate and the resulting residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) followed by conversion into an oxalate in a conventional manner to give the oxalate (35 mg) of the title compound as a pale yellow powder

(yield: 5.2%).

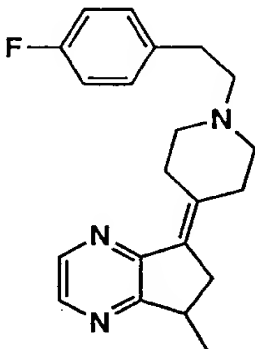
m.p. (oxalate): 196 - 198°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.83-1.91(4H, m), 2.90-3.05(6H, m), 3.18-3.27(2H, m), 3.38(2H, t, J=8Hz), 3.51-3.60(2H, m), 3.69-3.79(1H, m), 7.10(1H, d, J=5Hz), 7.14-7.19(2H, m), 7.30-7.34(2H, m), 7.83(1H, d, J=5Hz), 7.86(1H, s).

FAB-Mass: 326(MH+).

Example 265: Synthesis of 5-[1-(4-fluorophenethyl)piperidin-4-ylidenel-7-methyl-5,6-dihydrocyclopentapyrazine



5-Methyl-6,7-dihydro-5(H)-cyclopenta[B]pyrazine (2.82 g, CAS Registry No. 23747-48-0) was dissolved in tetrahydrofuran (30 ml). Under a stream of nitrogen, a 1.6 M solution (13.4 ml) of n-butyllithium in hexane was added dropwise into the resultant solution while cooling to -55°C or below. After stirring for 5 min, a solution of 1-(4-fluorophenethyl)-4-piperidone (3.72 g) in tetrahydrofuran (10 ml) was added

dropwise thereinto at the same temperature over 5 min. After stirring for 5 min, the reaction solution was allowed to warm to room temperature and water was added thereto. Then it was extracted with ethyl acetate and the organic layer was washed with brine and dried over magnesium sulfate. After evaporating the solvent, the resulting residue (6.5 g) was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) to give an isomer A (1.48 g) and another isomer B (2.94 g) of 5-[4-hydroxy-1-(4-fluorophenethyl)piperidin-4-yl]-7-methyl-5,6-dihydro-5H-cyclopentapyrazine each as an oil.

Isomer A:

$^1\text{H-NMR}$ (400 MHz, CDCl_3):

$\delta(\text{ppm})$ 1.40(3H, d, $J=6.8\text{Hz}$), 1.48-1.85(5H, m), 2.47-2.65(5H, m), 2.72-2.85(4H, m), 3.14-3.24(1H, m), 3.32-3.38(1H, m), 4.48(1H, s), 6.93-7.00(2H, m), 7.12-7.19(2H, m), 8.24(1H, dd, $J=1.2, 2.8\text{Hz}$), 8.36(1H, dd, $J=1.2, 2.8\text{Hz}$).

Isomer B:

$^1\text{H-NMR}$ (400 MHz, CDCl_3):

$\delta(\text{ppm})$ 1.33(3H, d, $J=7.2\text{Hz}$), 1.65-1.97(5H, m), 2.27-2.86(9H, m), 3.25-3.36(1H, m), 3.38-3.44(1H, m), 4.11(1H, s), 6.93-7.01(2H, m), 7.12-7.20(2H, m), 8.27(1H, dd, $J=0.8, 2.8\text{Hz}$), 8.36(1H, dd, $J=0.8, 2.8\text{Hz}$).

The above isomer A (1.48 g) was dissolved in acetic acid (10 ml). Then conc. sulfuric acid (2.0 ml) was added thereto

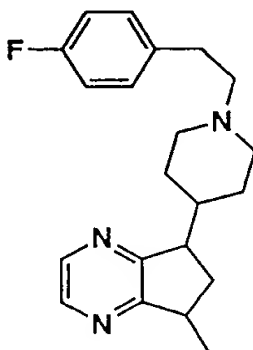
while cooling in a water bath and the resultant mixture was stirred at room temperature for 2 hr. The reaction solution was basified with 10% potassium carbonate and extracted with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. After evaporating the solvent, the resulting residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (680 mg) as an oil.

$^1\text{H-NMR}$ (400 MHz, CDCl_3):

$\delta(\text{ppm})$ 1.38(3H, d, $J=6.8\text{Hz}$), 2.12-2.40(1H, m), 2.45-2.50(2H, m), 2.56-2.69(6H, m), 2.79-2.86(2H, m), 3.06-3.14(1H, m), 3.20-3.30(1H, m), 3.33-3.39(1H, m), 6.94-7.00(2H, m), 7.15-7.19(2H, m), 8.18(1H, d, $J=2.7\text{Hz}$), 8.36(1H, dd, $J=0.8, 2.7\text{Hz}$).

FAB-Mass: 338(MH+).

Example 266: Synthesis of 5-[1-(4-fluorophenethyl)-piperidin-4-yl]-7-methyl-5,6-dihydro-5H-cyclopentapyrazine



5-[1-(4-Fluorophenethyl)piperidin-4-ylidene]-7-

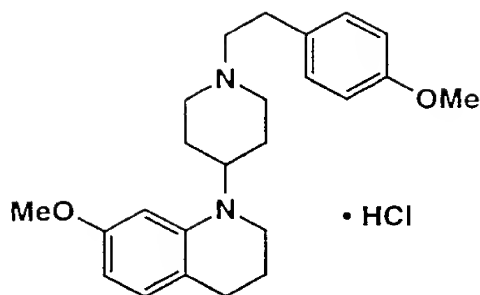
methyl-5,6-dihydrocyclopentapyrazine (300 mg) was dissolved in methanol (10 ml). After adding five drops of acetic acid thereinto, the resultant mixture was vigorously shaken in the presence of a palladium catalyst under a hydrogen gas pressure of 4.2 kg/cm² for 13 hr. After filtering off the catalyst, water was added to the reaction mixture followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. Then the solvent was evaporated to give the oily title compound (200 mg) as a mixture of stereoisomers (about 5 : 1).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.34(d, J=7.2Hz) and 1.40(d, J=6.8Hz)1 : 5 corresponding to 3H in total, 1.44-1.56(3H, m), 1.62-1.90(2H, m), 2.00-2.20(3H, m), 2.43-2.51(1H, m), 2.54-2.66(2H, m), 2.76-2.88(2H, m), 3.04-3.20(4H, m), 6.93-7.00(2H, m), 7.13-7.19(2H, m), 8.30(s) and 8.31(s)5 : 1 corresponding to 2H in total.

FAB-Mass: 340(MH⁺).

Example 267: Synthesis of 1-{1-[2-(4-methoxyphenyl)ethyl]piperidin-4-yl}-7-methoxy-1,2,3,4-tetrahydroquinoline hydrochloride



A solution of 1-(4-piperidiny1)-7-methoxy-1,2,3,4-tetrahydroquinoline (250 mg), 2-(4-methoxyphenyl)ethyl bromide (260 mg) and diisopropylethylamine (270 mg) in DMF (5 ml) was heated at 60°C for 12 hr under stirring. After the completion of the reaction, the reaction solution was cooled to room temperature and water was added thereto followed by extraction with ethyl acetate. The ethyl acetate layer was washed with brine and dried over magnesium sulfate. After evaporating the solvent, the resulting obtained residue was purified by silica gel column chromatography (toluene/acetone system) to give 1-{1-[2-(4-methoxyphenyl)ethyl]piperidin-4-yl}-7-methoxy-1,2,3,4-tetrahydroquinoline as an oil. This free compound was dissolved in ethyl acetate and 8.5% HCl/ethyl acetate was added thereto. The resulting hydrochloride was recrystallized from ethanol/ether to give the title compound (225 mg) (yield: 53%).

m.p.: 232 - 235°C.

¹H-NMR (400 MHz, DMSO-d₆):

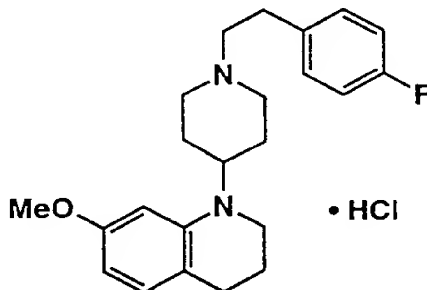
δ(ppm) 1.72-1.84(4H, m), 2.10-2.24(2H, m), 2.57(2H, t,

J=6.0Hz), 2.96-3.03(2H, m), 3.09(2H, t, J=5.6Hz), 3.11-3.21(4H, m), 3.58(2H, br-d), 3.66(3H, s), 3.71(3H, s), 3.90-4.00(1H, m), 6.11(1H, dd, J=8.4, 2.4Hz), 6.28(1H, d, J=2.4Hz), 6.78(1H, d, J=8.4Hz), 6.89(2H, d, J=8.4Hz), 7.18(2H, d, J=8.4Hz), 10.68-10.81(1H, br-s).

MS: 381(M+H)+.

Next, the procedure of Example 267 was repeated to give the products of Examples 268 to 274.

Example 268: 1-(1-[2-(4-Fluorophenyl)ethyl]piperidin-4-yl)-7-methoxy-1,2,3,4-tetrahydroquinoline hydrochloride



(Yield: 75%).

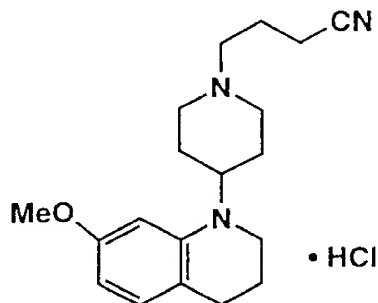
m.p.: 258°C (decomp.).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.74-1.84(4H, m), 2.23(2H, qd, J=12, 2Hz), 2.569(2H, t, J=6.4Hz), 3.04-3.23(6H, m), 3.57(2H, d, J=11.6Hz), 3.66(3H, s), 3.93-4.03(1H, m), 6.14(1H, dd, J=8, 1.6Hz), 6.32(1H, d, J=1.6Hz), 6.79(1H, d, J=7.6Hz), 7.16(2H, t, J=9.2Hz), 7.32(2H, dd, J=8.8, 5.6Hz), 11.05-11.20(1H, br-s).

MS: 369(M+H)+.

Example 269: 1-[1-(4-Cyanopropyl)piperidin-4-yl]-7-methoxy-1,2,3,4-tetrahydroquinoline hydrochloride



(Yield: 55%).

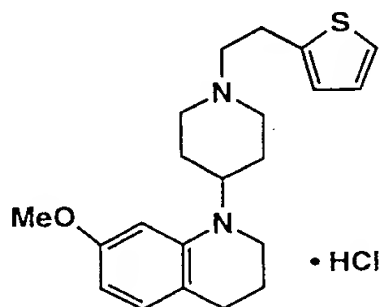
m.p.: 180 - 183°C (decomp.).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.71-1.82(4H, m), 1.97-2.12(2H, m), 2.15-2.28(2H, m), 2.56(2H, t, J=6.4Hz), 2.67(2H, t, J=7.2Hz), 2.99-3.18(6H, m), 3.51(2H, br-d, J=11.6Hz), 3.66(3H, s), 3.90-4.01(1H, m), 6.12(1H, dd, J=8.4, 1.0Hz), 6.29(1H, d, J=1.0Hz), 6.78(1H, d, J=8.4Hz), 10.94-11.12(1H, br-s).

MS: 314(M+H)+.

Example 270: 1-[1-[2-(2-Thienyl)ethyl]piperidin-4-yl]-7-methoxy-1,2,3,4-tetrahydroquinoline hydrochloride



(Yield: 35%).

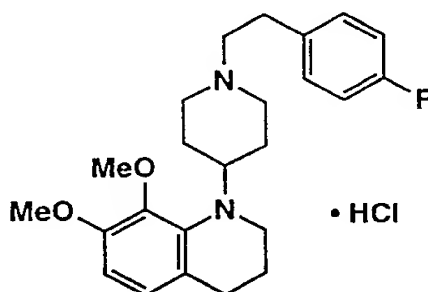
m.p.: 232 - 235°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.73-1.84(4H, m), 2.16-2.29(2H, m), 2.57(2H, t, J=6.4Hz), 3.10(2H, t, J=5.2Hz), 3.13-3.40(6H, m), 3.58(2H, br-d), 3.66(3H, s), 3.91-4.02(1H, m), 6.15(1H, br-d), 6.32(1H, br-s), 6.80(1H, d, J=8.0Hz), 6.97(1H, d, J=1.6Hz), 6.99(1H, d, J=5.2Hz), 7.40(1H, dd, J=5.2, 1.6Hz), 11.21-11.33(1H, br-s).

MS: 357(M+H)+.

Example 271: 1-{1-[2-(4-Fluorophenyl)ethyl]piperidin-4-yl}-7,8-dimethoxy-1,2,3,4-tetrahydroquinoline hydrochloride



(Yield: 82%).

m.p.: 213 - 215°C.

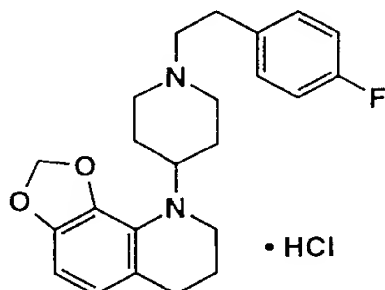
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.62-1.89(4H, m), 2.11-2.31(2H, m), 2.57-2.69(2H, m), 2.88-3.23(8H, m), 3.51-3.69(2H, m), 3.62(3H, s), 3.71(3H, s), 6.40-6.62(1H, br-d), 6.63-6.75(1H, br-d), 7.15(2H, t, J=8.8Hz), 7.29(2H, dd, J=7.6, 5.2Hz), 10.50-10.77(1H, br-s).

MS: 399(M+H)+.

Example 272: 1-{1-[2-(4-Fluorophenyl)ethyl]piperidin-4-

yl)-7,8-methylenedioxy-1,2,3,4-tetrahydroquinoline
hydrochloride



(Yield: 55%).

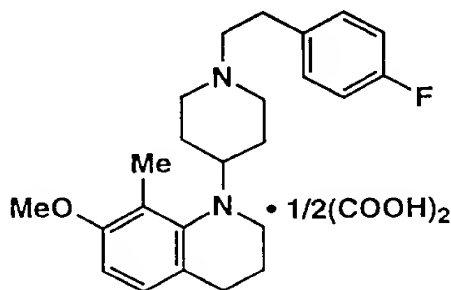
m.p.: 225 - 227°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.71-1.83(4H, m), 2.24(2H, qd, J=12.4, 3.2Hz),
2.58(2H, t, J=6.0Hz), 2.92-3.10(6H, m), 3.18-3.25(2H, m),
3.58(2H, br-d), 4.14-4.23(1H, m), 5.83(2H, s), 6.23(1H, d,
J=8.0Hz), 6.46(1H, d, J=8.0Hz), 7.16(2H, t, J=8.8Hz), 7.29(2H,
dd, J=8.8, 5.6Hz), 10.84-10.91(1H, m).

MS: 383(M+H)+.

Example 273: 1-((1-(2-(4-Fluorophenyl)ethyl)piperidin-4-
yl)-7-methoxy-8-methyl-1,2,3,4-tetrahydroquinoline oxalate



(Yield: 68%).

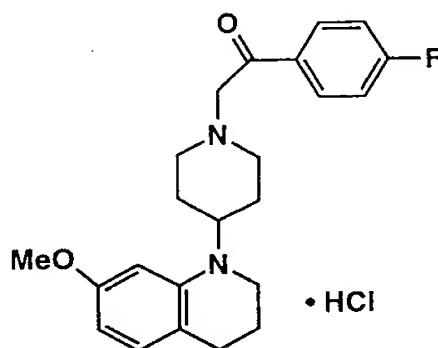
m.p.: 176 - 178°C.

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO}-d_6$):

$\delta(\text{ppm})$ 1.66-1.75(4H, m), 1.97-2.09(2H, m), 2.02(3H, s),
2.58(2H, t, $J=6.8\text{Hz}$), 2.79-3.22(9H, m), 3.40-3.51(2H, m),
3.71(3H, s), 6.47(1H, d, $J=8.4\text{Hz}$), 6.76(1H, d, $J=8.4\text{Hz}$),
7.13(2H, t, $J=8.8\text{Hz}$), 7.29(2H, dd, $J=11.2, 8.8\text{Hz}$).

MS: 383(M+H)+.

Example 274: 1-{1-[2-(4-Fluorophenyl)-2-oxoethyl]piperidin-4-yl}-7-methoxy-1,2,3,4-tetrahydroquinoline hydrochloride



(Yield: 60%).

m.p.: 153 - 155°C (decomp.).

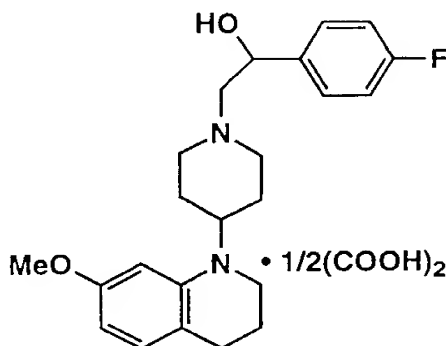
$^1\text{H-NMR}$ (400 MHz, $\text{DMSO}-d_6$):

$\delta(\text{ppm})$ 1.70-1.83(4H, m), 2.15-2.29(2H, m), 2.54(2H, t, $J=6.4\text{Hz}$), 3.08(2H, t, $J=6.0\text{Hz}$), 3.17-3.32(2H, m), 3.56(2H, br-d, $J=12.0\text{Hz}$), 3.62(3H, s), 3.92-4.03(1H, m), 4.98(2H, d, $J=4.4\text{Hz}$), 6.11(1H, dd, $J=7.2, 1.0\text{Hz}$), 6.32(1H, d, $J=1.0\text{Hz}$), 6.76(1H, d, $J=7.2\text{Hz}$), 7.41(2H, t, $J=8.8\text{Hz}$), 8.04(2H, dd, $J=8.8, 5.6\text{Hz}$).

10.22-10.39(1H, m).

MS: 383(M+H)+.

Example 275: 1-{1-[2-(4-Fluorophenyl)-2-hydroxyethyl]piperidin-4-yl}-7-methoxy-1,2,3,4-tetrahydroquinoline oxalate



Sodium borohydride (73 mg) was added at 0°C to a solution of 1-{1-[2-(4-fluorophenyl)-2-oxoethyl]piperidin-4-yl}-7-methoxy-1,2,3,4-tetrahydroquinoline (400 mg) in methanol (10 ml). The resultant mixture was stirred at the same temperature for 1 hr and then at room temperature for 1 hr. After the completion of the reaction, water was added to the reaction solution followed by extraction with ethyl acetate. The resulting residue was purified by column chromatography (hexane/ethyl acetate system) to give 1-{1-[2-(4-fluorophenyl)-2-hydroxyethyl]piperidin-4-yl}-7-methoxy-1,2,3,4-tetrahydroquinoline as an oil. This product was dissolved in ethanol and oxalic acid was added thereto. The resulting precipitate of salt was recrystallized form

ethanol/ether to give the title compound (280 mg) (yield: 68%).

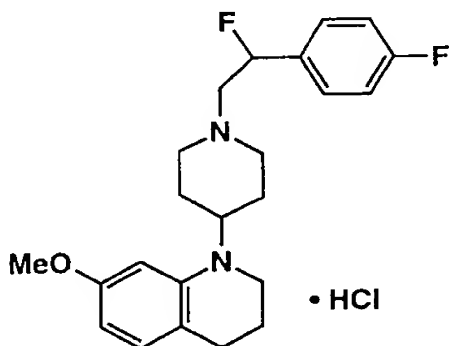
m.p.: 170 - 172°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.62-2.01(6H, m), 2.55(2H, t, J=6.4Hz), 2.58-2.90(4H, m), 3.09(2H, t, J=5.6Hz), 3.21-3.39(2H, m), 3.64(3H, s), 3.65-3.78(1H, m), 4.82-4.91(1H, m), 6.06(1H, dd, J=8.4, 2.4Hz), 6.20(1H, d, J=2.4Hz), 6.75(1H, d, J=8.4Hz), 7.17(2H, t, J=8.8Hz), 7.42(2H, dd, J=8.8, 6.0Hz).

MS: 385(M+H)+.

Example 276: 1-{1-[2-(4-Fluorophenyl)-2-fluoroethyl]piperidin-4-yl}-7-methoxy-1,2,3,4-tetrahydroquinoline hydrochloride



July 17/18
A solution of 1-{1-[2-(4-fluorophenyl)-2-hydroxyethyl]piperidin-4-yl}-7-methoxy-1,2,3,4-tetrahydroquinoline (250 mg) in methylene chloride (5 ml) was cooled to -78°C and diethylaminosulfur trifluoride (DAST, 0.1 ml) was added thereto. Then the reaction solution was stirred at the same temperature for 45 min. After the completion of

A18

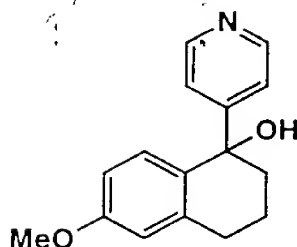
the reaction, saturated sodium bicarbonate was added to the reaction solution, which was then allowed to warm to room temperature under stirring. The reaction solution was extracted with ethyl acetate and the organic layer was dried over magnesium sulfate. After evaporating the solvent, the resulting residue was purified by silica gel column chromatography (hexane/hexane system) to give 1-{1-[2-(4-fluorophenyl)-2-fluoroethyl]piperidin-4-yl}-7-methoxy-1,2,3,4-tetrahydroquinoline as an oil. This product was dissolved in ethyl acetate. After adding ethyl acetate hydrochloric acid, the resulting salt was recrystallized from ethanol/ether to give the title compound (60 mg) (yield: 24%).
m.p.: 227 - 229°C.

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.72-1.88(4H, m), 2.10-2.34(2H, m), 2.57(2H, t, J=6.0Hz), 3.11(2H, t, J=5.2Hz), 3.17-3.80(6H, m), 3.66(3H, s), 3.93-4.03(1H, m), 6.13(1H, dd, J=8.0Hz), 6.31(1H, dd, J=50; 8.6Hz), 6.32(1H, s), 6.79(1H, d, J=8.0Hz), 7.31(2H, t, J=8.8, 6.0Hz), 7.53(2H, dd, J=8, 5.6Hz), 11.46-11.72(1H, m).

MS: 387 (M+H)+.

Example 277: Synthesis of 1-[2-(4-fluorophenyl)ethyl]-4-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)piperidine
(277-1) 4-(1-Hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)pyridine



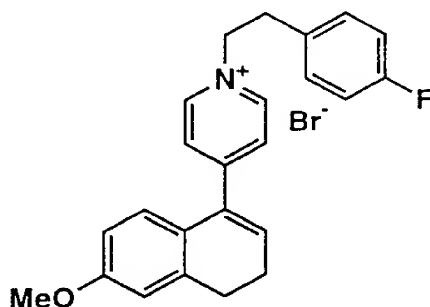
4-Bromopyridine hydrochloride 7.04 (1.0 equivalent) was partitioned between an aqueous solution of sodium hydroxide and diethyl ether. The organic layer was separated and dried over magnesium sulfate. Under nitrogen atmosphere, this solution was cooled to -78°C . Then a 1.6 M solution (25.0 ml, 1.0 equivalent) of n-butyllithium in hexane was added dropwise thereto and the resultant mixture was stirred for additional 30 min. Next, 6-methoxytetralone (7.049 g, 4.0 mmol) dissolved in tetrahydrofuran (50 ml) was added thereto and the resultant mixture was gradually warmed to room temperature while stirring continuously. After adding a saturated aqueous solution of ammonium chloride, the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. After evaporating the solvent under reduced pressure, the residue was reprecipitated from chloroform/n-hexane to give the title compound (4.019 g) as a pale yellowish brown powder (yield: 39.4%).

$^1\text{H-NMR}$ (400 MHz, $\text{DMSO}-d_6$):

$\delta(\text{ppm})$ 1.58-1.68 (1H, m), 1.91-2.00 (3H, m), 2.81 (2H, br-s),

3.72(3H, s), 5.69(1H, s), 6.65-6.70(2H, m), 6.77(1H, d, J=8.8Hz), 7.22(2H, d, J=6.0Hz), 8.45(2H, d, J =6.0Hz).

(277-2) 1-[2-(4-Fluorophenyl)ethyl]-4-(6-methoxy-3,4-dihydronaphthalen-1-yl)pyridinium bromide



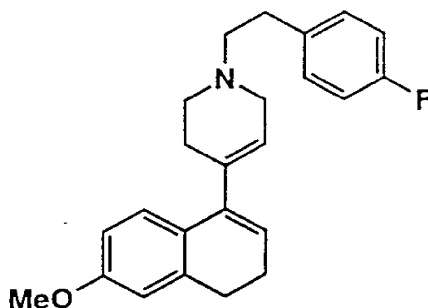
Under a nitrogen atmosphere, a mixture of 4-(1-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)pyridine (compound 1-1) (3.978 g, 15.6 mmol), 4-fluorophenethyl bromide (3.322 g, 1.05 equivalents) and acetonitrile (100 ml) was stirred at 80°C for 26 hr. Then 6.327 g (2.0 equivalents) of 4-fluorophenethyl bromide was further added thereto and the resultant mixture was stirred for additional 12 hr. After adding ethyl acetate and water, an insoluble precipitate was collected by filtration and air-dried at 50°C to give the title compound (5.785 g) as a pale brown powder (yield: 84.3%).

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 2.42-2.47(2H, m), 2.79(2H, br-t), 3.28(2H, br-t), 3.79(3H, s), 4.83(2H, t, J=7.4Hz), 6.54(1H, t, J=4.8Hz), 6.78(1H, dd, J=2.8, 8.4Hz), 6.86(1H, d, J=8.4Hz), 6.90(1H, d,

J=2.8Hz), 7.15-7.20(2H, m), 7.30-7.33(2H, m), 8.06(2H, d, J=6.8Hz), 8.96(2H, d, J=6.8Hz).

(277-3) 1-[2-(4-Fluorophenyl)ethyl]-4-(6-methoxy-3,4-dihydronaphthalen-1-yl)-1,2,3,6-tetrahydropyridine

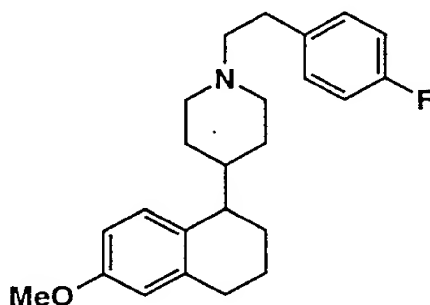


1-[2-(4-Fluorophenyl)ethyl]-4-(6-methoxy-3,4-dihydronaphthalen-1-yl)pyridinium bromide (compound 1-2) (5.710 g, 13 mmol) was dissolved in methanol (50 ml) and stirred under ice cooling. After adding 0.49 g of sodium borohydride thereto, the resultant mixture was stirred at room temperature for 2 hr. After removing the solvent under reduced pressure, water was added to the residue followed by extraction with ethyl acetate. The organic layer was washed with water and a saturated aqueous solution of sodium chloride and dried over magnesium sulfate. After evaporating the solvent under reduced pressure, the resulting residue was purified by silica gel column chromatography (n-hexane/ethyl acetate system) to give the title compound (4.169 g) as a pale brown viscous oil (yield: 88.5%).

¹H-NMR (400 MHz, CDCl₃):

δ (ppm) 2.21-2.27(2H, m), 2.33-2.38(2H, m), 2.66-2.74(6H, m), 2.84-2.88(2H, m), 3.19(2H, br-q), 3.80(1H, s), 5.71(1H, br-quintet), 5.84(1H, t, $J=4.8\text{Hz}$), 6.69(1H, dd, $J=2.4, 8.4\text{Hz}$), 6.73(1H, d, $J=2.4\text{Hz}$), 6.96-7.00(2H, m), 7.11(1H, d, $J=8.4\text{Hz}$), 7.17-7.20(2H, m).

(277-4) 1-[2-(4-Fluorophenyl)ethyl]-4-(6-methoxy-1,2,3,4-tetrahydrofuran-1-yl)piperidine



1-[2-(4-Fluorophenyl)ethyl]-4-(6-methoxy-3,4-dihydronaphthalen-1-yl)-1,2,3,6-tetrahydropyridine

(compound 1-3) (1.035 g, 2.85 mmol) was dissolved in methanol (100 ml). After adding 10% palladium-carbon (0.11 g), the mixture was catalytically reduced under atmospheric pressure for 12 hr. After filtering off the catalyst, 10% palladium-carbon (0.11 g) was added thereto again and catalytic reduction was carried out under atmospheric pressure for 6 hr. Then the catalyst was filtered off and the solvent was removed under reduced pressure to give the title compound (0.910 g) as a pale brown amorphous solid (yield: 93.9%).

This product was converted into a hydrochloride in a conventional manner followed by recrystallization from ethanol/diisopropyl ether to give the title compound as a colorless powder.

Free:

m.p.: 190 - 191°C (decomp.).

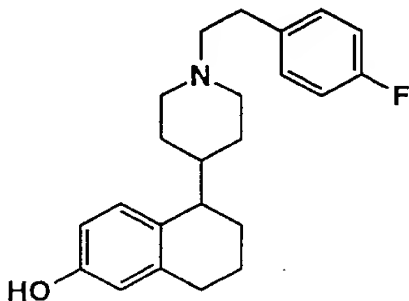
¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.58-1.90(8H, m), 2.27(2H, br-s), 2.66-2.64(4H, m), 2.84(2H, br-s), 3.01(2H, br-s), 3.33(2H, br-s), 3.77(3H, s), 6.62(1H, d, J=2.8Hz), 6.68(1H, dd, J=2.8, 8.4Hz), 6.96-6.70(2H, m), 7.03(1H, d, J=8.4Hz), 7.16-7.20(2H, m).

FAB-MS: [M+H]⁺: m/z=368.

Example 278: Synthesis of 1-[2-(4-fluorophenyl)ethyl]-4-[6-(2-hydroxy)ethoxy-1,2,3,4-tetrahydronaphthalen-1-yl]piperidine

(278-1) 1-[2-(4-Fluorophenyl)ethyl]-4-[6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl]piperidine



47% hydrobromic acid (45 ml) was added to 1-[2-(4-fluorophenyl)ethyl]-4-(6-methoxy-1,2,3,4-tetrahydro-

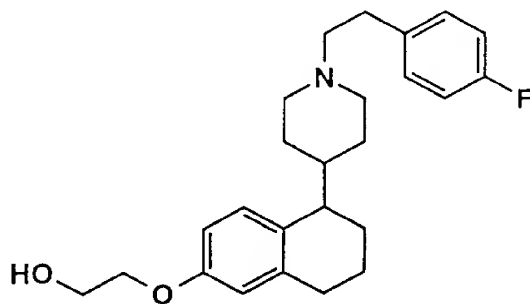
55% sodium hydride (0.055 g, 1.1 equivalents) was washed with n-hexane and suspended in N,N-dimethylformamide (3 ml) followed by stirring under ice cooling. To the resultant solution was added 1-[2-(4-fluorophenyl)ethyl]-4-[6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl]piperidine (compound 2-1) (2.718 g, 7.57 mmol) dissolved in N,N-dimethylformamide (1 ml) and the resultant mixture was stirred at room temperature for 30 min. Then the resultant mixture was ice cooled again followed by addition of (2-t-butyltrimethylsilyloxy)ethanol (0.410 g, 1.5 equivalents) dissolved in N,N-dimethylformamide (1 ml). Under a nitrogen atmosphere, the resulting mixture was stirred at 50°C for 25 hr. After adding water, the reaction solution was extracted with ethyl acetate. The extract was washed successively with water and brine and dried over magnesium sulfate. After removing the solvent under reduced pressure, the resulting residue was purified by silica gel column chromatography (n-hexane/ethyl acetate system) to give the title compound (0.371 g) as a colorless viscous oil (yield: 63.4%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 0.10(6H, s), 0.91(9H, s), 1.36-1.98(12H, m), 2.40-2.54(2H, m), 2.60-2.79(4H, m), 2.99-3.06(2H, m), 3.93-3.96(2H, m), 3.98-4.01(2H, m), 6.61(1H, d, J=2.4Hz), 6.68(1H, dd, J=2.4, 8.4Hz), 6.93-6.97(2H, m), 7.04(1H, d, J=8.4Hz),

7.12-7.16(2H, m).

(278-3) 1-[2-(4-Fluorophenyl)ethyl]-4-[6-(2-hydroxy)-ethoxy-1,2,3,4-tetrahydronaphthalen-1-yl]piperidine



1-[2-(4-Fluorophenyl)ethyl]-4-[6-(2-t-butyltrimethylsilyloxy)ethoxy-1,2,3,4-tetrahydronaphthalen-1-yl]piperidine (compound 2-2) (0.350 g, 0.684 mmol) was dissolved in tetrahydrofuran (5 ml). After adding a 1.0 M solution (821 ml, 1.2 equivalents) of tetra-n-butylammonium fluoride in tetrahydrofuran thereto, the resultant mixture was stirred at room temperature for 9.5 hr. After adding water, the reaction solution was extracted with ethyl acetate. The extract was washed successively with water (for three times) and brine and dried over magnesium sulfate. After evaporating the solvent, the resulting residue was purified by silica gel column chromatography (chloroform/methanol system) to give the title compound (0.242 g) as a colorless viscous oil (yield: 89.0%).

This product was converted into a hydrochloride in a conventional manner and recrystallized from

ethanol/diisopropyl ether to give the title compound as a colorless powder.

Free:

$^1\text{H-NMR}$ (400 MHz, CDCl_3):

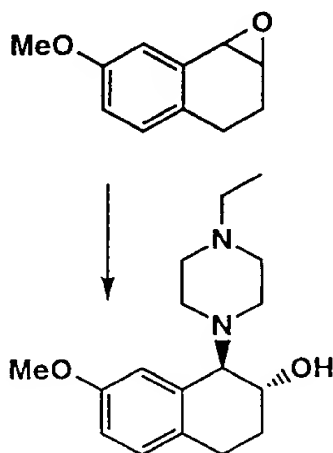
δ (ppm) 1.21-1.88(12H, m), 2.41-2.45(2H, m), 2.51-2.70(4H, m), 2.90-2.97(2H, m), 3.83(2H, t, $J=9.2\text{Hz}$), 3.95(2H, t, $J=9.2\text{Hz}$), 6.53(1H, d, $J=2.8\text{Hz}$), 6.60(1H, dd, $J=2.8, 8.8\text{Hz}$), 6.83-6.87(2H, m), 6.96(1H, d, $J=8.8\text{Hz}$), 7.02-7.05(2H, m).

FAB-MS: $[\text{M}+\text{H}]^+$: $m/z=398$.

m.p.: 213 - 215°C (decomp.).

Example 279: Synthesis of trans-1-(4-ethylpiperazin-1-yl)-7-methoxy-2-(4-trifluoromethylphenoxy)-1,2,3,4-tetrahydronaphthalene

(279-1) trans-1-(4-Ethylpiperazin-1-yl)-2-hydroxy-7-methoxy-1,2,3,4-tetrahydronaphthalene



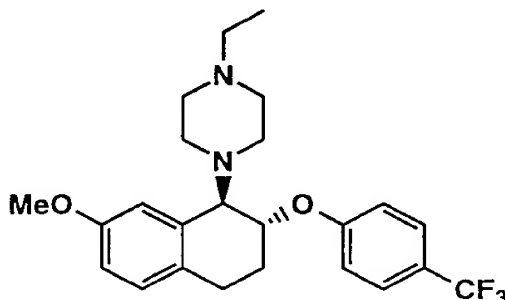
7-Methoxy-3,4-dihydronaphthalene-1,2-oxide (5.28 g)

synthesized in accordance with the method described in Tetrahedron, 33, 85 - 94. was dissolved in n-butanol (100 ml). After adding ethylpiperazine (3.42 g), the resultant mixture was heated under reflux for 12 hr. After removing the solvent under reduced pressure, the residue was recrystallized from ethyl acetate (5 ml) and ether (80 ml). The crystals were collected by filtration and washed with ether to give the title compound (6.88 g) as pale yellow crystals (yield: 79%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.73-1.85(1H, m), 2.09-2.16(1H, m), 2.48(4H, br-s), 2.77(2H, m), 2.91(4H, br-s), 3.16(1H, br-s), 3.68(1H, d, J=8.5Hz), 3.78(3H, s), 3.95(1H, ddd, J=3.0Hz, 8.5Hz, 10.5Hz), 6.71(1H, br-d), 6.99(1H, d, J=10.0Hz), 7.12(1H, br-s).

(279-2) trans-1-(4-Ethylpiperazin-1-yl)-7-methoxy-2-(4-trifluoromethoxy)-1,2,3,4-tetrahydronaphthalene



A solution of potassium t-butoxide (247 mg) and 4-fluorobenzotrifluoride (492 mg) in dimethylformamide (1 ml) was added slowly at room temperature to a solution of trans-1-(4-ethylpiperazin-1-yl)-2-hydroxy-7-methoxy-1,2,3,4-

tetrahydronaphthalene (435 mg) in dimethylformamide (3 ml) and the resultant mixture was stirred for 4 hr. After adding water (50 ml), the reaction mixture was extracted with ethyl acetate (50 ml) for three times. The organic phase was washed with water (50 ml) twice and brine (50 ml) once and dried over anhydrous magnesium sulfate followed by concentration under reduced pressure. The resulting residue was purified by silica gel column chromatography (NH-DM2035, Fuji Silysia Chemical Ltd., hexane/ethyl acetate system) to give the title compound (190 mg) as a colorless oil (yield: 29%).

m.p. (oxalate): 207 - 210°C.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.03(3H, t, J=7.0Hz), 1.85-1.96(1H, m), 2.15-2.22(1H, m), 2.39(2H, q, J=7.0Hz), 2.42(4H, br-s), 2.70(2H, br-s), 2.77(2H, br-s), 2.80(2H, t, J=6.0Hz), 3.81(3H, s), 4.05(1H, d, J=7.5Hz), 4.79(1H, m), 6.76(1H, dd, J=3.0Hz, 8.0Hz), 6.97(2H, d, J=8.5Hz), 7.02(1H, d, J=8.0Hz), 7.33(1H, d, J=3.0Hz), 7.53(2H, d, J=8.5Hz).

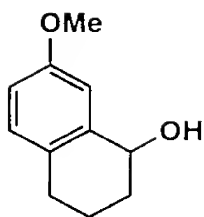
FAB-Mass: 435(MH+).

Example 280: Synthesis of 1-{4-[2-(4-

fluorophenyl)ethyl]piperazin-1-yl}-7-methoxy-1,2,3,4-

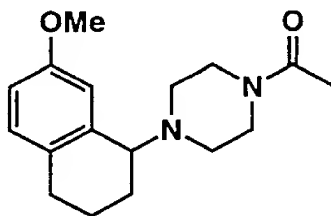
tetrahydronaphthalene hydrochloride

(280-1) 1-Hydroxy-7-methoxy-1,2,3,4-tetrahydronaphthalene



7-Methoxy-1,2,3,4-tetrahydronaphthalen-1-one (5 g) was dissolved in methanol and sodium tetrahydroborate (1.3 g) was added thereto at 0°C. After reacting at room temperature for 2 hr, the reaction solution was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with water, dried and concentrated under reduced pressure to give the title compound (5.19 g) as a colorless oil.

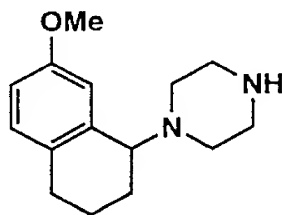
(280-2) 1-(4-Acetylpiperazin-1-yl)-7-methoxy-1,2,3,4-tetrahydronaphthalene



1-Hydroxy-7-methoxy-1,2,3,4-tetrahydronaphthalene (5.19 g) was reacted with thionyl chloride (4.3 ml) in ether at room temperature for 3 hr. Then the reaction solution was partitioned between ether and water. The ether layer was washed successively with water, a saturated aqueous solution of sodium bicarbonate and brine, dried and concentrated under reduced pressure. The resulting residue, 1-acetylpiperazine and

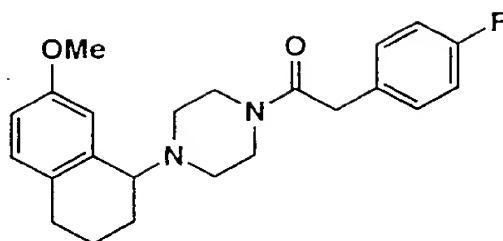
potassium carbonate were heated under reflux in acetone for 10 hr. Then the reaction solution was filtered and insolubles were washed with methylene chloride. After concentrating the filtrate under reduced pressure, the resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system) to give the title compound (3.0 g) as a pale yellow oil.

(280-3) 7-Methoxy-1-(piperazin-1-yl)-1,2,3,4-tetrahydro-naphthalene



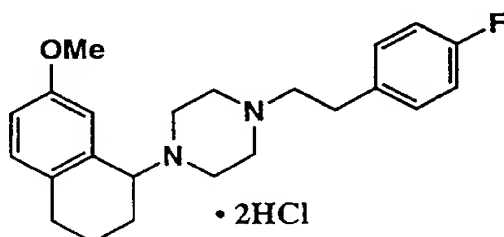
1-(4-Acetylpiperazin-1-yl)-7-methoxy-1,2,3,4-tetrahydronaphthalene (0.85 g) was dissolved in ethanol (10 ml). After adding an 8 N aqueous solution (3 ml) of sodium hydroxide, the resultant mixture was heated under reflux for 3 hr. Then the liquid reaction mixture was concentrated under reduced pressure and the residue was purified by NH-silica gel column chromatography (ethyl acetate) to give the title compound (0.6 g) as a pale brown oil.

(280-4) 1-[4-(4-Fluorophenylacetyl)piperazin-1-yl]-7-methoxy-1,2,3,4-tetrahydronaphthalene



7-Methoxy-1-(piperazin-1-yl)-1,2,3,4-tetrahydro-naphthalene (0.6 g) was reacted in methylene chloride for 2 hr with an acid chloride prepared from 4-fluorophenylacetic acid (0.44 g) and thionyl chloride (0.21 ml). Then the liquid reaction mixture was partitioned between methylene chloride and water, extracted with methylene chloride, dried and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (toluene/acetone system) to give the title compound (0.56 g) as an oil.

(280-5) 1-[4-[2-(4-Fluorophenyl)ethyl]piperazin-1-yl]-7-methoxy-1,2,3,4-tetrahydronaphthalene



1-[4-(4-Fluorophenylacetyl)piperazin-1-yl]-7-methoxy-1,2,3,4-tetrahydronaphthalene (0.41 g) and lithium aluminum hydride (0.05 g) were heated under reflux in THF (15 ml) for 6 hr. Next, the reaction solution was cooled and water (50 ml),

a 5 N aqueous solution (50 ml) of sodium hydroxide and further water (150 ml) were successively added thereto. After stirring the resultant mixture at room temperature for 1 hr, the resulting precipitate was filtered through celite and washed with THF. The filtrate was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (toluene/acetone system) to give the title compound (0.38 g) as an oil.

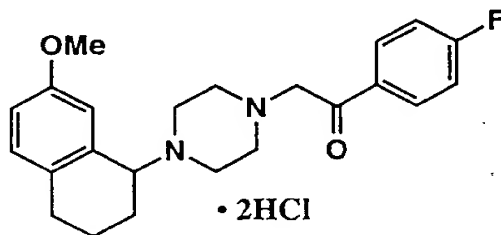
m.p.: 205°C (decomp.).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.60-1.70(2H, m), 1.93-2.02(2H, m), 2.48-2.81(14H, m), 3.76-3.83(1H, m), 3.79(3H, s), 6.71(1H, dd, J=8.4, 2.8Hz), 6.96(2H, t, J=8.4Hz), 7.12-7.19(3H, m), 7.32(1H, d, J=2.8Hz).

FAB-Mass: 269(MH+).

Example 281: Synthesis of 1-{4-[2-(4-fluorophenyl)-2-oxoethyl]piperazin-1-yl}-7-methoxy-1,2,3,4-tetrahydronaphthalene hydrochloride



7-Methoxy-1-(piperazin-1-yl)-1,2,3,4-tetrahydronaphthalene (0.27 g), 4-fluorophenacyl bromide

(0.24 g) and diisopropylethylamine (0.43 g) were dissolved in DMF (15 ml) and reacted at room temperature for 12 hr. Then the liquid reaction mixture was distributed between ethyl acetate and water. The ethyl acetate layer was washed with water, dried and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate/n-hexane system) to give an oil (0.34 g). This product was converted into a hydrochloride in a conventional manner to give the title compound as a white powder.

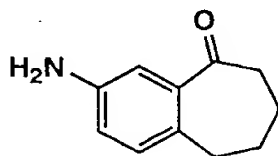
m.p.: 194°C (decomp.).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.60-1.69(2H, m), 1.92-2.01(2H, m), 2.53-2.68(8H, m), 3.76(2H, s), 3.79(3H, s), 6.70(1H, dd, J=8.4, 2.8Hz), 6.97(1H, d, J=8.4Hz), 7.09-7.15(2H, m), 7.31(1H, d, J=2.8Hz), 8.04-8.10(2H, m).

FAB-Mass: 383(MH+).

Example 282-1: Synthesis of 8-aminobenzosuberone



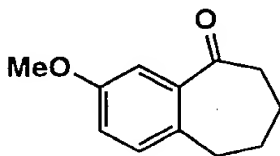
Ammonium nitrate (24 g) was added in portions at -10°C to a solution of benzosuberone (40 g) and trifluoroacetic anhydride (85 ml) in chloroform (400 ml) and the resultant

mixture was stirred at room temperature overnight. The reaction solution was concentrated under reduced pressure, then a saturated aqueous solution of sodium bicarbonate and ethyl acetate were added thereto and the layers were separated. The organic layer was washed with brine and dried over anhydrous magnesium sulfate followed by purifying by silica gel column chromatography (hexane/ethyl acetate system). Then palladium carbon (5 g) and ethanol (300 ml) were added thereto and catalytic reduction was carried out under hydrogen atmosphere at 50°C. After stirring overnight, the catalyst was filtered off and the residue was concentrated under reduced pressure and purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (10 g) (yield: 24%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.71-1.89(4H, m), 2.67-2.72(2H, m), 2.80-2.85(2H, m), 3.70(2H, br-s), 6.76(1H, dd, J=8, 3Hz), 6.97(1H, d, J=8Hz), 7.04(1H, t, J=3Hz).

Example 282-2: Synthesis of 8-methoxybenzosuberone



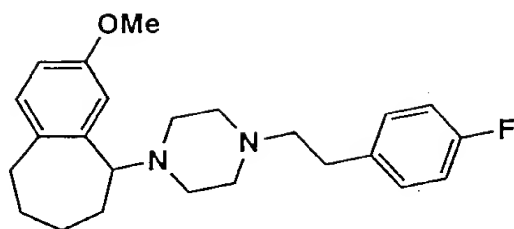
An aqueous solution (15 ml) of sodium nitrite (9.0 g) was added dropwise into a mixture of 8-aminobenzosuberone (4.0 g), conc. sulfuric acid (3 ml) and water (47 ml) at 5°C or below.

After 30 min, the reaction solution was added dropwise into a saturated aqueous solution (25 ml) of copper sulfate heated to 90°C and stirred for 30 min. After cooling the reaction solution to room temperature, ethyl acetate was added thereto and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. To the residue were added methyl iodide, potassium carbonate and dimethylformamide and the resultant mixture was stirred at room temperature for 7 hr. After concentrating the reaction solution under reduced pressure, water and ethyl acetate were added thereto and the layers were separated. The organic layer was washed with brine and dried over anhydrous magnesium sulfate followed by purifying by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (3.5 g) (yield: 80%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.78-1.90(4H, m), 2.70-2.75(2H, m), 2.87-2.92(2H, m), 3.81(3H, s), 6.99(1H, dd, J=8, 3Hz), 7.11(1H, d, J=8Hz), 7.29(1H, t, J=3Hz).

Example 282-3: Synthesis of 1-(4-fluorophenethyl)-4-(2-methoxybenzocycloheptan-9-yl)piperazine



Sodium borohydride (0.7 g) was added to a solution of 8-methoxybenzosuberone (3.5 g) in ethanol (40 ml) and the resultant mixture was stirred at room temperature for 1 hr. Then the reaction solution was concentrated under reduced pressure and diluted with a saturated aqueous solution of sodium bicarbonate and ethyl acetate and the layers were separated. The organic layer was washed with brine and dried over magnesium sulfate. After evaporating the solvent, toluene (50 ml) and thionyl chloride (2.4 g) were added to the residue. The resultant mixture was stirred for 2 hr and then concentrated under reduced pressure. To the residue were added dimethylformamide (50 ml), 1-(4-fluorophenethyl)piperazine (2.1 g) synthesized in accordance with the method described in JP-A 54-92979 and triethylamine (0.7 g) and the resultant mixture was stirred at 100°C for 3 hr. After concentrating the liquid reaction mixture under reduced pressure, a saturated aqueous solution of sodium bicarbonate and ethyl acetate were added thereto and the layers were separated. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The resulting residue was purified by silica gel column

chromatography (methylene chloride/ethanol system) followed by conversion into a hydrochloride in a conventional manner to give the hydrochloride (230 mg) of the title compound as a white powder (yield: 11%).

m.p. (hydrochloride): 188 - 190°C.

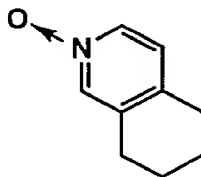
¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.20-1.35(1H, m), 1.50-1.65(2H, m), 1.74-1.98(4H, m), 2.06-2.19(2H, m), 2.21-2.67(4H, m), 2.96-3.06(3H, m), 3.20-3.35(3H, m), 3.49-3.80(2H, m), 3.74(3H, s), 6.69-6.89(2H, m), 7.00-7.09(1H, m), 7.12-7.20(2H, m), 7.28-7.40(2H, m).

FAB-Mass: 383(MH+).

Example 283: Synthesis of 5-{4-[2-(4-fluorophenyl)-ethyl]piperazin-1-yl}-5,6,7,8-tetrahydroisoquinoline hydrochloride

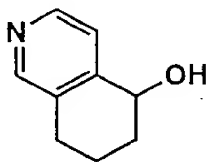
(283-1) 5,6,7,8-Tetrahydroisoquinoline-2-oxide



5,6,7,8-Tetrahydroisoquinoline (10 g) was added to methylene chloride (100 ml) and a 10% aqueous solution (100 ml) of sodium carbonate. Under vigorous stirring, a 70% solution of m-chloroperbenzoic acid (20 g) in methylene chloride (100 ml) was dropped thereinto at 0°C. Then the reaction solution was extracted with methylene chloride. The methylene chloride

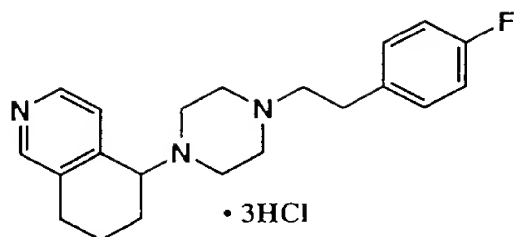
layer was washed with brine, dried and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol system) to give the title compound (7.50 g) as a colorless oil.

(283-2) 5,6,7,8-Tetrahydroisoquinolin-5-ol



5,6,7,8-Tetrahydroisoquinoline-2-oxide (7.50 g) was dissolved in acetic anhydride (30 ml). After reacting at 120°C for 6 hr, the reaction solution was concentrated under reduced pressure. Next, a 10% aqueous solution (30 ml) of hydrochloric acid was added to the residue followed by heating at 100°C for 2 hr. The reaction solution was cooled, basified with 5 N sodium hydroxide and extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried. After evaporating the solvent under reduced pressure, the resulting residue was purified by silica gel column chromatography (ethyl acetate) to give the title compound (1.90 g).

(283-3) 5-{4-[2-(4-Fluorophenyl)ethyl]piperazin-1-yl}-5,6,7,8-tetrahydroisoquinoline hydrochloride



5,6,7,8-Tetrahydroisoquinolin-5-ol (1.90 g),
methanesulfonyl chloride (1.48 g) and triethylamine (5.0 ml)
were reacted in THF (50 ml) at 0°C for 6 hr. The reaction
solution was partitioned between ethyl acetate and a saturated
aqueous solution of sodium bicarbonate. The ethyl acetate
layer was washed with water, dried and concentrated under
reduced pressure to give a pale yellow oil. This product was
dissolved in DMF followed by addition of 4-[2-(4-
fluorophenyl)ethyl]piperazine (2.0 g) and potassium carbonate
(2.0 g). After reacting for 12 hr, the reaction solution was
concentrated under reduced pressure and the obtained residue
was purified by silica gel column chromatography (methylene
chloride/methanol system) to give a pale yellow oil (0.71 g).
Next, this product was converted into a hydrochloride in a
conventional manner to give the title compound (0.52 g) as a
white powder.

m.p.: 174 - 176°C.

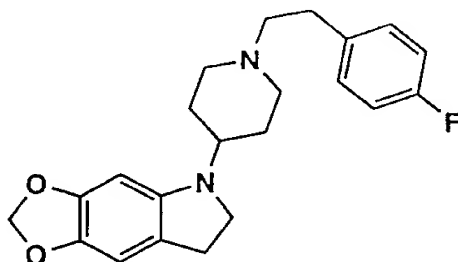
¹H-NMR (400 MHz, D₂O):

δ(ppm) 1.77(2H, m), 1.99-2.16(2H, m), 2.87(2H, m), 3.03(4H,
m), 3.38(4H, m), 4.19(1H, m), 7.05(2H, t, J=8.4Hz), 7.26(2H,

dd, J=8.4, 7.2Hz), 8.28(1H, d, J=8.0Hz), 8.43(1H, d, J=8.0Hz), 8.45(1H, s).

FAB-Mass: 340(MH+).

Example 284: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-5,6-methylenedioxyindoline



1-(4-Fluorophenethyl)-4-(3,4-methylenedioxyphenyl)-aminopiperidine (10 g) synthesized in accordance with the method described in Referential Example 1 of JP-B 40-6347 was treated as in Example 106 to give the hydrochloride (330 mg) of the title compound as dark red prismatic crystals (yield: 2.8%).

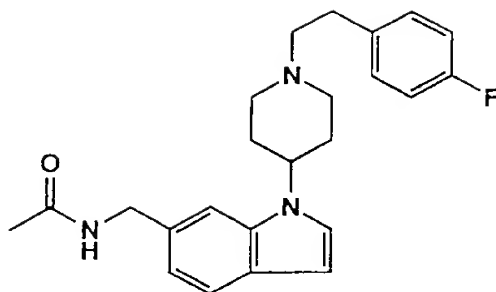
m.p. (hydrochloride): 229°C (decomp.)

¹H-NMR (400 MHz, DMSO-d₆):

δ(ppm) 1.80-2.09(4H, m), 2.72-2.85(2H, m), 2.99-3.19(4H, m), 3.19-3.35(4H, m), 3.55-3.61(3H, m), 5.82(2H, s), 6.44(1H, s), 6.71(1H, s), 7.12-7.20(2H, m), 7.29-7.38(2H, m).

FAB-Mass: 369(MH+).

Example 285: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindole



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindoline (7.5 g) obtained in Example 133 was dissolved in acetone (500 ml) at 50°C. To the resultant solution was added active manganese dioxide (35.6 g) in portions under stirring. The resulting suspension was heated under reflux for 1.5 hr, then filtered through celite and washed with acetone. The filtrate was concentrated under reduced pressure and the resulting pale yellow solid was recrystallized from ethyl acetate to give the title compound (4.2 g) as a white powder (yield: 56%).

¹H-NMR (400 MHz, DMSO-d₆):

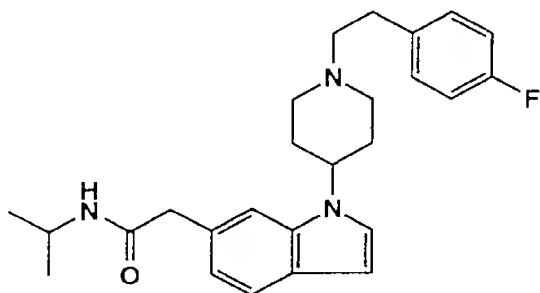
δ(ppm) 1.86(s, 3H), 1.88-2.04(m, 4H), 2.23(dt, J=11.2, 2.4Hz, 2H), 2.55-2.62(m, 2H), 2.74-2.81(m, 2H), 3.09(br-d, 2H), 4.26-4.36(m, 1H), 4.33(d, J=5.6Hz, 2H), 6.41(d, J=3.2Hz, 1H), 6.94(d, J=7.2Hz, 1H), 7.08-7.15(m, 2H), 7.26-7.33(m, 2H), 7.41(br-s, 1H), 7.45-7.49(m, 2H), 8.26-8.32(m, 1H).

m.p.: 127 - 128°C.

Mass: FAB+ 394(M+H).

Example 286: Synthesis of 1-[1-(4-fluorophenethyl)-

piperidin-4-yl]-6-(N-isopropylcarbamoylmethyl)indole



A suspension of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(isopropylcarbamoylmethyl)indoline (1 g) obtained in Example 151 and active manganese dioxide (4 g) in 1,2-dichloroethane (100 ml) was heated under reflux for 1.5 hr, then filtered through celite and concentrated under reduced pressure. The resulting pale yellow solid was recrystallized from ethyl acetate to give the title compound (0.4 g) as a white powder (yield: 40%).

¹H-NMR (400 MHz, CDCl₃):

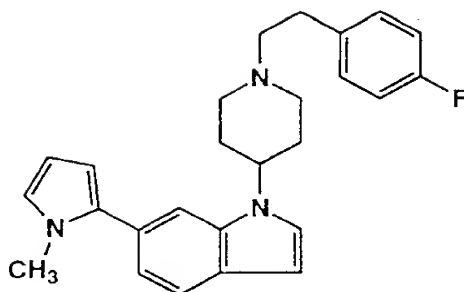
δ(ppm) 1.04(d, J=6.0Hz, 6H), 2.04-2.18(m, 4H), 2.25-2.40(m, 2H), 2.63-2.74(m, 2H), 2.80-2.91(m, 2H), 3.15-3.28(m, 2H), 3.68(s, 2H), 4.02-4.12(m, 1H), 4.20-4.31(m, 1H), 5.20-5.32(m, 1H), 6.53(d, J=3Hz, 1H), 6.95-7.02(m, 3H), 7.18-7.21(m, 2H), 7.26-7.28(m, 2H), 7.61(d, J=8Hz, 1H).

m.p.: 146 - 148°C.

Mass: ESI 422(M+).

Example 287: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1-methylpyrrol-2-

yl)indole



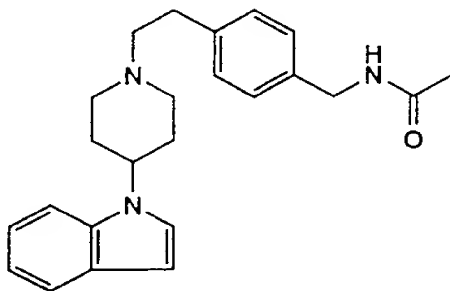
1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-bromoindole (0.2 g) was dissolved in toluene (2.50 ml). Next, 1-methyl-2-tributylstannylpyrrole (1.44 g) synthesized in accordance with the method described in Tetrahedron Lett., 4407 (1986). with the use of 1-methylpyrrole and tributyltin chloride was added thereto and the resultant mixture was heated under reflux for 3 hr under nitrogen atmosphere. After adding ethyl acetate, the mixture was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (0.115 g) as a yellow oil (yield: 57.28%).

$^1\text{H-NMR}$ (400 MHz, CDCl_3):

δ (ppm) 1.92-1.99(4H, m), 2.05-2.13(2H, m), 2.47-2.51(2H, m), 2.64-2.68(2H, m), 3.32(2H, br-d), 3.50(3H, s), 4.05-4.13(1H, m), 6.16-6.19(2H, m), 6.38(1H, d, $J=3.6\text{Hz}$), 6.57(1H, t, $J=2.2\text{Hz}$), 6.82(2H, t, $J=8.6\text{Hz}$), 6.98-7.03(3H, m), 7.11(1H, d, $J=3.6\text{Hz}$), 7.23(1H, s), 7.48(1H, d, $J=8.8\text{Hz}$).

ESI-Mass: 402.

Example 288: Synthesis of 1-[1-(4-acetamidomethylphenethyl)piperidin-4-yl]indole



A suspension of 1-[1-(4-acetamidomethylphenethyl)piperidin-4-yl]indoline (0.80 g) obtained in Example 36 and active manganese dioxide (1.32 g) in chloroform (30 ml) was heated under reflux for 6 hr with vigorous stirring. Then the reaction mixtures were filtered through celite and the residue was washed with chloroform. The filtrate was concentrated under reduced pressure and the obtained residue was crystallized from a solvent mixture of ethyl acetate with hexane to give the title compound (0.64 g) as a white powder (yield: 80.4%).

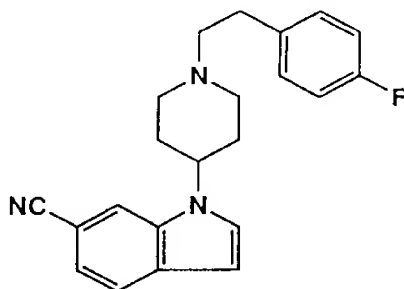
m.p.: 133 - 134°C.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 2.02(3H, s), 2.06-2.35(5H, m), 2.64-2.73(2H, m), 2.82-2.90(2H, m), 3.15-3.25(2H, br-d), 4.22-4.32(1H, m), 4.41(2H, d, J=5.6Hz), 6.53(1H, d, J=3.6Hz), 7.07-7.13(1H, m), 7.18-7.26(5H, m), 7.38(1H, d, J=8.0Hz), 7.63(2H, d, J=8.0Hz).

FAB-Mass: 376(MH+).

Example 289: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-cyanoindole



1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-cyanoindoline (0.50 g) obtained in Example 124 and active manganese dioxide (1.00 g) were treated as in Example 288 to give the title compound (0.42 g) as a white powder (yield: 83.8%).

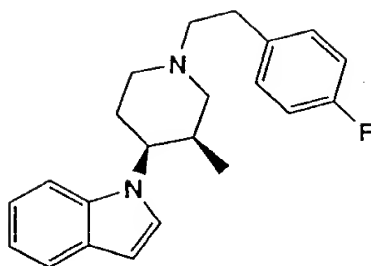
m.p.: 131 - 132°C.

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 2.06-2.16(3H, m), 2.25-2.34(2H, m), 2.64-2.70(2H, m), 2.79-2.87(2H, m), 3.16-3.24(2H, m), 4.21-4.31(1H, m), 4.41(2H, d, J=5.6Hz), 6.60(1H, d, J=3.2Hz), 6.97-7.03(2H, m), 7.16-7.22(2H, m), 7.33(1H, dd, J=8.0, 1.2Hz), 7.44(1H, d, J=3.2Hz), 7.67(2H, d, J=8.0Hz), 7.73(1H, br-s).

FAB-Mass: 378(MH+).

Example 290: Synthesis of cis-1-[1-(4-fluorophenethyl)-3-methylpiperidin-4-yl]indole



cis-1-[1-(4-Fluorophenethyl-3-methylpiperidin-4-yl]indoline was synthesized in a similar manner to the one of Example 79-4 by starting with indoline (560 mg), 1-[2-(4-fluorophenyl)ethyl]-3-methyl-4-piperidone (1.19 mg) and sodium triacetoxyborohydride (2.40 g). As the by-product in this reaction, the title compound (30 mg) was obtained as a white amorphous substance (yield: 3%).

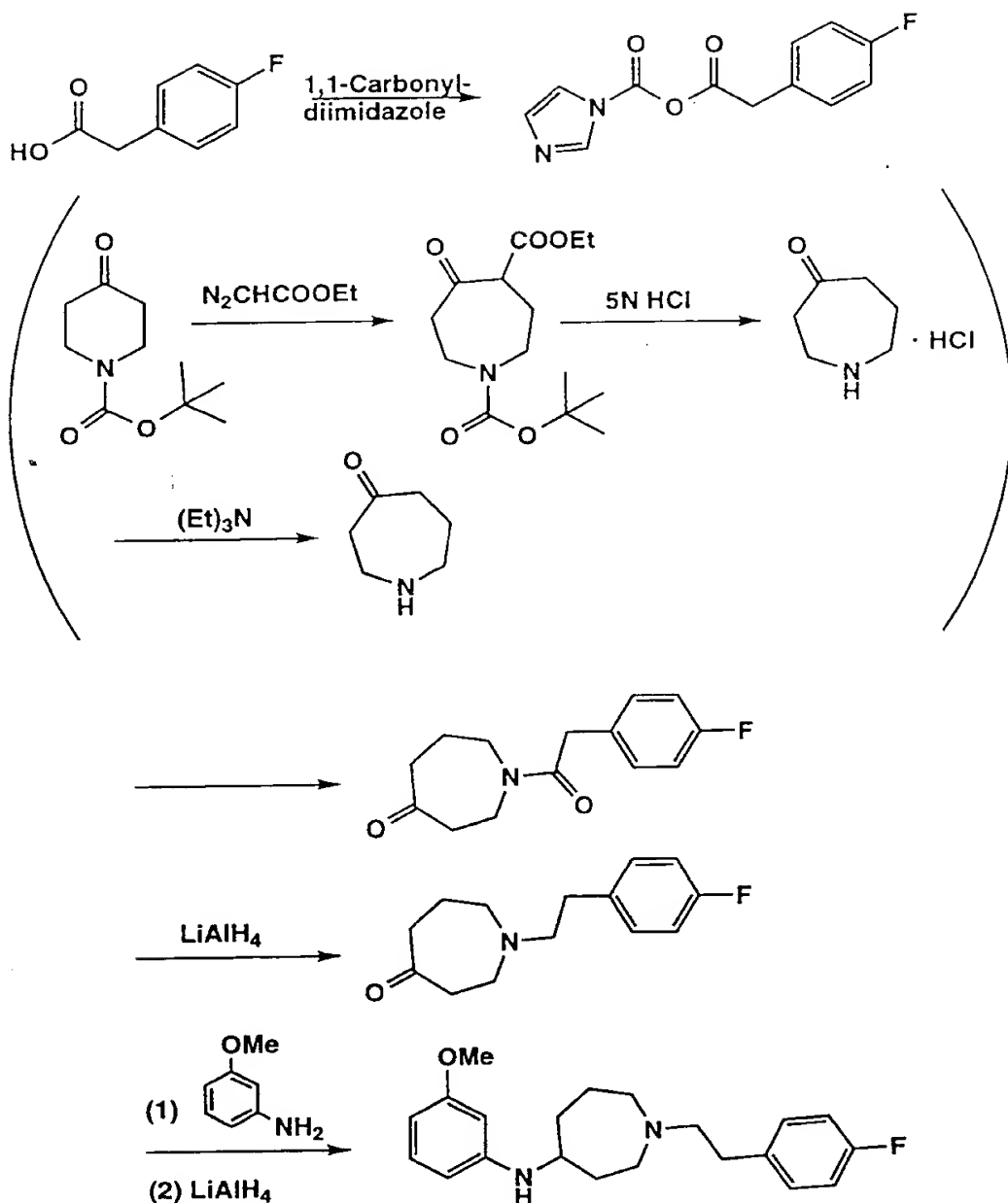
$^1\text{H-NMR}$ (400 MHz, CDCl_3):

δ (ppm) 0.80(3H, d, $J=6.5\text{Hz}$), 1.88(1H, br-d), 2.26(1H, dt, $J=12.0, 3.5\text{Hz}$), 2.35-2.67(5H, m), 2.74-2.82(2H, m), 2.89(1H, br-d), 3.14(1H, br-d), 4.46(1H, dt, $J=120.5, 4.0\text{Hz}$), 6.49(1H, d, $J=3.1\text{Hz}$), 6.98(2H, br-t), 7.10(1H, br-d), 7.16-7.22(4H, m), 7.36(2H, d, $J=8.0\text{Hz}$), 7.64(2H, d, $J=8.0\text{Hz}$).

FAB-Mass: 337(MH+).

Example 291: Synthesis of 1-[1-(4-fluorophenethyl)homo-
piperidin-4-yl]-6-methoxyindoline

(291-1) 1-(4-Fluorophenethyl)-4-(3-methoxyphenylamino)-
homopiperidine



4-Fluorophenylacetic acid (1.5 g) was dissolved in tetrahydrofuran (44 ml). To the resultant solution was added N,N-carbonyldimidazole (1.6 g) and the resultant mixture was stirred at room temperature for 15 min. Next, 4-homopiperidone hydrochloride (1.0 g) synthesized in accordance with the method

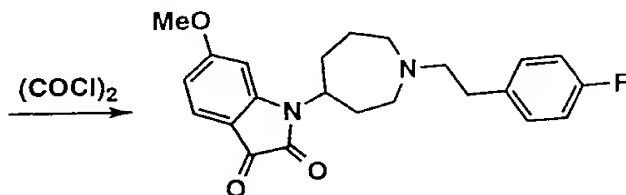
described in Synth. Commun., 1249 (1992). and triethylamine (1.2 ml) were successively added thereto followed by stirring at room temperature for 12 hr. After adding water, the reaction solution was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran and lithium aluminum hydride was added thereto under ice cooling. Next, the resultant mixture was heated under reflux and treated in a conventional manner. The resulting product was purified by silica gel column chromatography (hexane/ethyl acetate system) to give a brown oil.

The above product and m-anisidine (0.39 ml) were treated as in Example 1 to give a yellow oil. This product was dissolved in tetrahydrofuran (30 ml). Under ice cooling, lithium aluminum hydride (0.72 g) was added thereto and the resultant mixture was heated under reflux for 2.5 hr. Under ice cooling, water (0.72 ml), a 5 N aqueous solution (0.72 ml) of sodium hydroxide and further water (2.2 ml) were successively added thereto and the resulting solid was filtered off. The filtrate was concentrated under reduced pressure and the obtained residue was purified by silica gel column chromatography (ethyl acetate/methanol system) to give the title compound (1.348 g) as a brown oil (yield: 44.6%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.62-1.79(5H, m), 1.95-2.04(1H, m), 2.59-2.67(2H, m), 2.70-2.85(6H, m), 3.66(1H, m), 3.76(3H, s), 4.02(1H, br-s), 6.00(1H, t, J=2.4Hz), 6.12(1H, ddd, J=0.8, 2.4, 8.0Hz), 6.23(1H, ddd, J=0.8, 2.4, 8.0Hz), 6.98(2H, t, J=8.8Hz), 7.05(1H, t, J=8.0Hz), 7.16(2H, dd, J=4.2, 8.8Hz).

(291-2) 1-(4-Fluorophenethyl)-4-(6-methoxyisatin-1-yl)homopiperidine

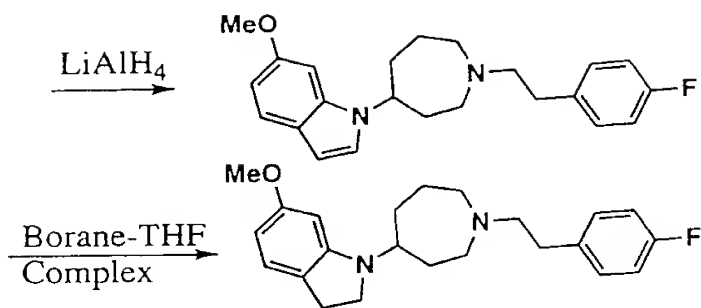


1-(4-Fluorophenethyl)-4-(3-methoxyphenylamino)homopiperidine (1.148 g) was treated in accordance with the method described in J. Prakt. Chem., 137 (1922). to give the title compound (1.203 g) as an orange oil (yield: 90.6%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.83-2.00(3H, m), 2.10(2H, m), 2.78(7H, br-s), 2.87(2H, br-s), 3.93(3H, s), 3.43(1H, m), 4.40(1H, br-s), 6.52(1H, s), 6.53(1H, d, J=8.8Hz), 6.99(1H, t, J=8.8Hz), 7.18(1H, dd, J=5.6, 8.8Hz), 7.59(1H, d, J=8.8Hz).

(291-3) 1-[1-(4-Fluorophenethyl)homopiperidin-4-yl]-6-methoxyindoline



1-(4-Fluorophenethyl)-4-(6-methoxyisatin-1-yl)homopiperidine (0.4 g) was dissolved in tetrahydrofuran (1.0 ml). Under nitrogen atmosphere, a 2.0 M solution (4.0 ml) of borane-tetrahydrofuran complex in tetrahydrofuran was added dropwise thereinto in a water bath followed by heating under reflux for 3 hr. The reaction solution was ice cooled and water was added thereto. Next, the reaction solution was partitioned between water and ethyl acetate and the organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in pyridine (5.0 ml) and stirred at room temperature for 11 hr. After adding water, the reaction solution was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Then the resulting residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) to give 1-(4-fluorophenethyl)-4-(6-methoxyindol-1-yl)homopiperidine as a yellow oil. Then this product was treated as in Production Example 64 to give

the free title compound (0.095 g) as a yellow oil (yield: 27.2%).

Next, this product was treated with oxalic acid in a conventional manner to give the oxalate of the title compound as a hygroscopic solid.

Free:

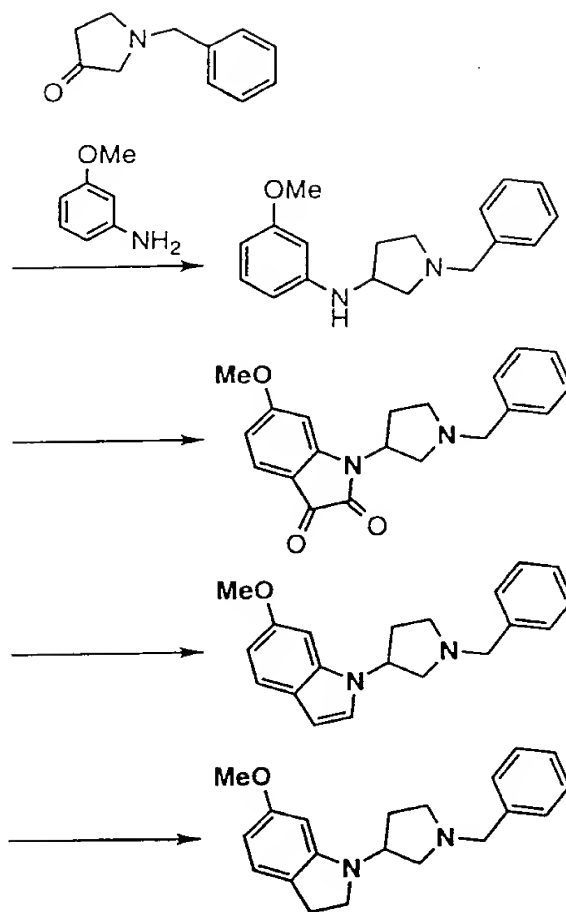
¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.61-1.99(6H, m), 2.66-2.90(10H, m), 3.38(2H, dt, J=1.6, 8.6Hz), 3.63(1H, m), 3.76(3H, s), 6.00(1H, d, J=2.4Hz), 6.12(1H, dd, J=2.4, 7.6Hz), 6.92(1H, d, J=7.6Hz), 6.97(2H, t, J=8.4Hz), 7.15(2H, dd, J=5.6, 8.4Hz).

ESI-Mass: 369.1

Example 292: Synthesis of 1-[1-(4-fluorophenethyl)-pyrrolidin-3-yl]-6-methoxyindoline

(292-1) 1-Benzyl-3-(6-methoxyindolin-1-yl)pyrrolidine



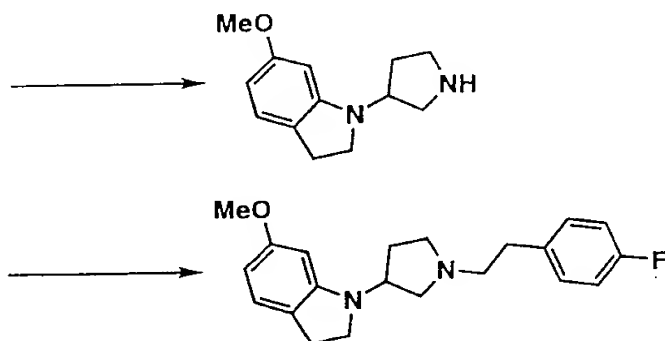
1-Benzyl-3-pyrrolidone (10.0 g) and *m*-anisidine (0.39 ml) were treated as in Example 1 to give a brown oil. Then this product was treated as in the above (291-2) to give red crystals. Subsequently, these crystals were treated as in the above (291-3) to give the title compound (2.301 g) as a pale yellow oil (yield: 13.1%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 2.00(1H, br-s), 2.21(1H, br-s), 2.68-2.98(4H, br-s), 2.86(1H, t, J=8.0Hz), 3.42(1H, q, J=8.0Hz), 3.60-3.90(2H,

br-s), 3.75(3H, s), 4.24(1H, br-s), 6.09(1H, d, J=2.4Hz), 6.16(1H, dd, J=2.4, 8.0Hz), 6.92(1H, d, J=8.0Hz), 7.27-7.42(5H, m).

(292-2) 1-[1-(4-Fluorophenethyl)pyrrolidin-3-yl]-6-methoxyindoline



1-Benzyl-3-(6-methoxyindolin-1-yl)pyrrolidine (0.5 g) was treated as in Tetrahedron Lett., 1567 (1977). to give a yellow oil. Then this product and 4-fluorophenethyl bromide (0.15 g) were treated as in Example 2 to give the free title compound (2.301 g) as a pale yellow oil (yield: 13.1%).

Next, this free compound was treated with oxalic acid in acetone in a conventional manner to give the oxalate of the title compound as a hygroscopic amorphous solid.

Oxalate:

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6):

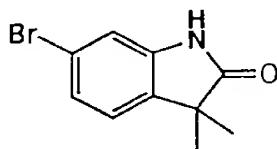
$\delta(\text{ppm})$ 1.89(1H, m), 2.08(1H, m), 2.62-3.06(10H, m), 3.32(2H, t, J=8.2Hz), 3.65(3H, s), 4.30(1H, m), 6.10(1H, dd, J=2.0, 8.0Hz), 6.15(1H, d, J=2.0Hz), 6.87(1H, d, J=8.0Hz),

7.10(2H, t, J=8.4Hz), 7.27(2H, dd, J=5.4, 8.4Hz).

ESI-Mass: 341.1.

Example 293: Synthesis of 3,3-dimethyl-1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-bromoindoline

(293-1) 3,3-Dimethyl-6-bromoindolin-2-one



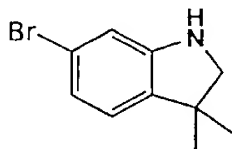
A solution (50 ml) of 6-bromoindolin-2-one (3.18 g) in THF was cooled to -78°C and 1.5 M lithium diisopropylamide (20 ml) was added dropwise thereinto followed by stirring for 15 min. After adding methyl iodide (0.92 ml), the reaction mixture was brought to room temperature and stirred for 1 hr. Then the reaction solution was cooled to -78°C again and 1.5 M lithium diisopropylamide (10 ml) was added dropwise thereinto followed by stirring for 15 min. After adding methyl iodide (0.92 ml), the reaction solution was brought to room temperature with stirring. Then a saturated aqueous solution of ammonium chloride was added thereto and the resultant mixture was extracted with ethyl acetate. The residue was washed with hexane to give the title compound (3.35 g) as a white amorphous solid (yield: 93.0%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.38(6H, s), 7.05(1H, d, J=8.0Hz), 7.096(1H, d,

J=1.6Hz), 7.169(1H, d, J=1.6Hz), 8.41(1H, m).

(293-2) 3,3-Dimethyl-6-bromoindoline

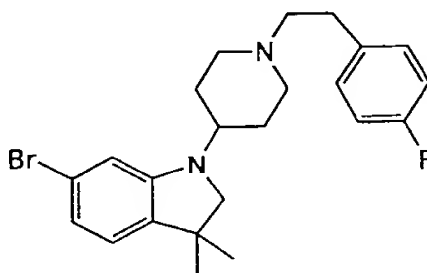


A borane-dimethylsulfide complex (3 ml) was added dropwise into a solution (80 ml) of 3,3-dimethyl-6-bromoindolin-2-one (3.35 g) in toluene under stirring at 60°C. Then the reaction mixtures were heated under reflux for 3 hr. Under ice cooling, a 5 N aqueous solution (20 ml) of sodium hydroxide was added thereto and the resultant mixture was stirred at room temperature for 30 min. Then the reaction mixtures were extracted with ethyl acetate, washed with water and brine and dried. The extract was concentrated under reduced pressure to give the title compound (3.10 g) as a yellow oil (yield: 98.3%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.28(6H, s), 3.35(2H, s), 6.83-6.91(3H, m).

(293-3) 3,3-Dimethyl-1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-bromoindoline



3,3-Dimethyl-6-bromoindoline (3.10 g), 1-[2-(4-fluorophenyl)ethyl]-4-piperidone (2.81 g) and triacetoxylated sodium borohydride (5.70 g) were treated as in Example 16 to give the title compound (2.72 g) as a white amorphous solid (yield: 49.8%).

¹H-NMR (400 MHz, CDCl₃):

δ(ppm) 1.24(6H, s), 1.80(4H, br-s), 2.13-2.24(2H, m), 2.58-2.67(2H, m), 2.79-2.86(2H, m), 3.11-3.21(2H, m), 3.17(2H, s), 3.28-3.40(1H, m), 6.44(1H, s), 6.72(1H, d, J=8.0Hz), 6.80(1H, d, J=8.0Hz), 6.93-7.01(2H, m), 7.13-7.20(2H, m).

FAB-Mass: 432(MH+).

Example 294: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(ethylcarbamoylmethyl)indole

A suspension of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(ethylcarbamoylmethyl)indoline (0.41 g) obtained in Example 149 and active manganese dioxide (0.40 g) in chloroform (30 ml) was vigorously stirred at 50°C for 6 hr. Then the reaction mixtures were filtered through celite and the residue was washed with chloroform. After concentrating the filtrate under reduced pressure, the residue was recrystallized from chloroform/hexane to give the title compound (0.33 g) as white needles (yield: 89.5 %).

m.p.: 159.6 - 160.1°C.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 1.02(3H,t,J=7.2Hz), 2.07-

2.13(4H,m), 2.25-2.32(2H,m), 2.64-2.68(2H,m), 2.81-
2.85(2H,m), 3.17-3.26(4H,m), 3.70(2H,s), 4.21-4.29(1H,m),
5.40(1H,br-t), 6.53(1H,d,J=3.2Hz), 6.95-7.01(3H,m), 7.17-
7.21(2H,m), 7.26-7.28(2H,m), 7.61(1H,d,J=8.0Hz).

ESI-Mass ; 408(MH+).

Example 295: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-
4-yl]-6-[N-(cyclopropylcarbamoyl)methyl]indole

A suspension of 1-[1-(4-fluorophenethyl)piperidin-
4-yl]-6-[(cyclopropylcarbamoyl)methyl]indoline (0.04 g)
obtained in Example 154 and active manganese dioxide (0.04 g)
in chloroform (30 ml) was vigorously stirred at 50°C for 10 hr.
Then the reaction mixtures were filtered through celite and the
residue was washed with chloroform. After concentrating the
filtrate under reduced pressure, the residue was recrystallized
from chloroform/hexane to give the title compound (0.03 g) as
a white powder (yield: 81.9 %).

m.p.: 156.4 - 156.8°C.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 0.34-0.38(2H,m), 0.68-
0.73(2H,m), 2.06-2.14(4H,m), 2.25-2.32(2H,m), 2.62-
2.68(3H,m), 2.81-2.85(2H,m), 3.18(2H,br-d), 3.68(2H,s),
4.20-4.28(1H,m), 5.50(1H,br-s), 6.52(1H,d,J=3.2Hz),
6.93(1H,dd,J=1.4,8.2Hz), 6.97-7.01(2H,m), 7.17-7.20(2H,m),
7.25-7.27(2H,m), 7.60(1H,d,J=8.2Hz).

ESI-Mass ; 420(MH+).

Example 296: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[N-(isobutylcarbamoyl)methyl]indole

A suspension of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[(isobutylcarbamoyl)methyl]indoline (0.07 g) obtained in Example 152 and active manganese dioxide (0.07 g) in chloroform (30 ml) was vigorously stirred at 50°C overnight. Then the reaction mixtures were filtered through celite and the residue was washed with chloroform. After concentrating the filtrate under reduced pressure, the residue was recrystallized from chloroform/hexane to give the title compound (0.05 g) as a white powder (yield: 70.0 %).

m.p.: 131.8 - 132.2°C.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 0.79(6H,d,J=6.8Hz), 1.61-1.71(1H,m), 2.07-2.13(4H,m), 2.24-2.31(2H,m), 2.64-2.68(2H,m), 2.81-2.85(2H,m), 3.01(2H,t,J=6.4Hz), 3.18(2H,br-d), 3.72(2H,s), 4.20-4.28(1H,m), 5.46(1H,br-t), 6.53(1H,d,J=2.8Hz), 6.96-7.01(3H,m), 7.17-7.20(2H,m), 7.26-7.27(2H,m), 7.61(1H,d,J=8.0Hz).

ESI-Mass ; 436(MH+).

Example 297: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(n-propylcarbamoylmethyl)indole

A suspension of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[(n-propylcarbamoyl)methyl]indoline (0.04 g) obtained in Example 150 and active manganese dioxide (0.08 g)

in chloroform (30 ml) was vigorously stirred at 50°C overnight. Then the reaction mixtures were filtered through celite and the residue was washed with chloroform. After concentrating the filtrate under reduced pressure, the residue was recrystallized from chloroform/hexane to give the title compound (0.03 g) as white needles (yield: 84.6 %).

m.p.: 131.1 - 131.9°C.

¹H-NMR(400MHz, CDCl₃) ; δ (ppm) 0.81(3H,t,J=7.4Hz), 1.41(2H,tq,J=7.4,7.4Hz), 2.07-2.12(4H,m), 2.25-2.31(2H,m), 2.64-2.68(2H,m), 2.81-2.85(2H,m), 3.71(2H,s), 4.20-4.28(1H,m), 5.43(1H,br-t), 6.53(1H,d,J=3.2Hz), 6.96-7.01(3H,m), 7.17-7.21(2H,m), 7.25-7.27(2H,m), 7.61(1H,d,J=8.0Hz).

ESI-Mass ; 422(MH+).

Example 298: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(tetramethylenecarbamoylmethyl)indole oxalate

A suspension of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(tetramethylenecarbamoylmethyl)indoline (0.08 g) obtained in Example 155 and active manganese dioxide (0.07 g) in chloroform (30 ml) was vigorously stirred at 50°C overnight. Then the reaction mixtures were filtered through celite and the residue was washed with chloroform. After concentrating the filtrate under reduced pressure, the free compound (0.06 g) of the title compound was obtained as a pale brown viscous compound

(yield: 87.0 %).

Next, this free compound was converted into an oxalate in a conventional manner, which was then reprecipitated from methanol/diethyl ether to give the title compound as a colorless powder.

Free compound:

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 1.78-1.93(4H,m), 2.09(4H,br-s), 2.25-2.33(2H,m), 2.64-2.68(2H,m), 2.81-2.85(2H,m), 3.17(2H,br-d), 3.45-3.51(4H,m), 3.78(2H,s), 4.24-4.32(1H,m), 6.49(1H,d,J=3.0Hz), 6.97-7.01(3H,m), 7.17-7.20(2H,m), 7.22(1H,d,J=3.0Hz), 7.38(1H,s), 7.55(1H,d,J=8.0Hz).

Oxalate:

m.p.: 171.5 - 172.1°C.

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 1.72-1.79(2H,m), 1.83-1.90(2H,m), 2.09-2.21(4H,m), 2.92-3.18(6H,m), 3.29(2H,t,J=7.0Hz), 3.49(2H,t,J=7.0Hz), 3.49-3.56(2H,m), 3.70(2H,s), 4.58(1H,br-s), 6.45(1H,d,J=3.2Hz), 6.93(1H,dd,J=1.2,8.4Hz), 7.16-7.20(2H,m), 7.33-7.37(2H,m), 7.39-7.42(2H,m), 7.46(1H,d,J=8.4Hz).

ESI-Mass ; 434(MH+).

Example 299: Synthesis of 1-[1-(2,4-difluorophenethyl)piperidin-4-yl]-6-carbamoylmethylindole

A suspension of 1-[1-(2,4-difluorophenethyl)-piperidin-4-yl]-6-carbamoylmethylindoline (0.05 g) obtained

in Example 225 and active manganese dioxide (0.10 g) in chloroform (30 ml) was vigorously stirred at 50°C overnight. Then the reaction mixtures were filtered through celite and the residue was washed with chloroform. After concentrating the filtrate under reduced pressure, the residue was recrystallized from chloroform/hexane to give the title compound (0.02 g) as a white powder (yield: 41.7 %).

m.p.: 156.9 - 157.8°C.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.03-2.12(4H,m), 2.25-2.31(2H,m), 2.63-2.67(2H,m), 2.84-2.88(2H,m), 3.17(2H,br-d), 4.22-4.30(1H,m), 5.54(2H,br-s), 6.52(1H,dd,J=0.8,3.2Hz), 6.88(1H,dt,J=1.2,8.6Hz), 7.10(1H,ddd,J=0.8,7.0,8.0Hz), 7.13-7.22(2H,m), 7.24(1H,d,J=3.6Hz), 7.38(1H,dd,J=0.4,8.4Hz), 7.62-7.65(1H,m).

ESI-Mass ; 398(MH+).

Example 300: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-hydroxyethyl)carbamoylmethylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (0.20 g) obtained in Example 146 was dissolved in N,N-dimethylformamide (5 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.104 g) and the resultant mixture was stirred under nitrogen atmosphere at room temperature for 15 min. Next, ethanolamine (320 ml) was added thereto and the mixture was further stirred overnight. After

evaporating the solvent under reduced pressure, water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give a pale brown viscous oil (0.15 g).

This residue was dissolved in chloroform (30 ml) and manganese dioxide (0.31 g) was added thereto. After stirring the resultant mixture at 50°C overnight, the manganese dioxide was filtered off and the solvent was evaporated under reduced pressure. Then the residue was recrystallized from chloroform/n-hexane to give the title compound (0.13 g) as a pale yellow powder.

m.p.: 140.0 - 141.2°C.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.08-2.21(4H,m), 2.28(2H,br-t), 2.64-2.68(2H,m), 2.81-2.85(2H,m), 3.19(2H,br-d), 3.35-3.39(2H,m), 3.67(2H,t,J=5.0Hz), 3.74(2H,s), 4.19-4.28(1H,m), 5.90(1H,br-t), 6.51(1H,br-d), 6.96-7.02(3H,m), 7.17-7.21(2H,m), 7.25(1H,d,J=3.2Hz), 7.31(1H,br-s), 7.61(1H,d,J=8.4Hz).

ESI-Mass ; 424(MH+).

Example 301: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-dimethylcarbamoylmethylindole oxalate

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (0.19 g) obtained in Example 146 was

$\frac{d}{dt} \left(\frac{\partial L}{\partial \dot{x}} \right) = \frac{\partial L}{\partial x}$, $\frac{d}{dt} \left(\frac{\partial L}{\partial \dot{y}} \right) = \frac{\partial L}{\partial y}$, $\frac{d}{dt} \left(\frac{\partial L}{\partial \dot{z}} \right) = \frac{\partial L}{\partial z}$

$\frac{d}{dt} \left(\frac{\partial L}{\partial \dot{x}} \right) = \frac{\partial L}{\partial x}$

$\frac{d}{dt} \left(\frac{\partial L}{\partial \dot{x}} \right) = \frac{\partial L}{\partial x}$

[illegible]

6.91(1H,d,J=8.2Hz), 7.15-7.20(2H,m), 7.33-7.37(2H,m),
7.40(2H,br-s), 7.47(1H,d,J=8.2Hz).

ESI-Mass ; 408(MH+).

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Example 302: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(4-hydroxypiperidin-1-ylcarbonylmethyl)indole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (0.21 g) obtained in Example 146 was dissolved in N,N-dimethylformamide (5 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.11 g) and the resultant mixture was stirred in a nitrogen atmosphere at room temperature for 15 min. Next, 4-hydroxypiperidine (0.56 g) was added thereto and the mixture was further stirred overnight. After evaporating the solvent under reduced pressure, water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give a pale brown viscous oil (0.18 g).

This residue (0.13 g) was dissolved in chloroform (30 ml) and manganese dioxide (0.33 g) was added thereto. After stirring the resultant mixture at 50°C for 10 hr, the manganese dioxide was filtered off and the solvent was removed under reduced pressure. Then the residue was recrystallized from chloroform/n-hexane to give the title compound (0.16 g) as colorless micaceous flakes.

m.p.: 190.5 - 192.2°C (decomp.).

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 1.22-1.50(2H,m), 1.62-1.69(1H,m), 1.82-1.89(1H,m), 2.05-2.11(4H,m), 2.24-2.31(2H,m), 2.63-2.67(2H,m), 2.80-2.84(2H,m), 3.15-3.24(4H,m), 3.76-3.88(2H,m), 3.88(2H,s), 4.11-4.17(2H,m), 4.21-4.29(1H,m), 6.49(1H,d, $J=3.6\text{Hz}$), 6.95-7.01(3H,m), 7.17-7.20(2H,m), 7.22(1H,d, $J=3.6\text{Hz}$), 7.30(1H,s), 7.56(1H,d, $J=8.4\text{Hz}$).

ESI-Mass ; 464(MH+).

Example 303: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[bis(2-hydroxyethyl)]carbamoylmethylindole oxalate

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (0.20 g) obtained in Example 146 was dissolved in N,N-dimethylformamide (5 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.10 g) and the resultant mixture was stirred under nitrogen atmosphere at room temperature for 15 min. Next, diethanolamine (0.56 g) dissolved in N,N-dimethylformamide (1 ml) was added thereto and the mixture was further stirred overnight. After evaporating the solvent under reduced pressure, water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give a pale brown viscous oil (0.16 g).

This residue was dissolved in chloroform (30 ml) and manganese dioxide (0.30 g) was added thereto. After stirring the resultant mixture at 50°C overnight, the manganese dioxide was filtered off and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol system) to give a free compound (0.10 g) of the title compound as a pale brown viscous oil, which was then converted into an oxalate in a conventional manner.

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 2.10(2H,br-d), 2.29(2H,br-q), 3.98-3.08(4H,m), 3.16-3.21(2H,m), 3.39(2H,br-t), 3.45-3.58(8H,m), 3.83(2H,s), 4.57-4.65(1H,m), 6.45(1H,d,J=3.2Hz), 6.91(1H,d,J=8.0Hz), 7.17(2H,br-t), 7.33-7.37(2H,m), 7.40(2H,br-s), 7.47(1H,d,J=8.0Hz).

ESI-Mass ; 468(MH+).

Example 304: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1,3-dihydroxypropan-2-yl)carbamoylmethylindole oxalate

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (0.23 g) obtained in Example 146 was dissolved in N,N-dimethylformamide (5 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.11 g) and the resultant mixture was stirred under nitrogen atmosphere at room temperature for 15 min. Next, 2-amino-1,3-propanediol

(Serinol, 0.27 g) was added thereto and the mixture was further stirred overnight. After evaporating the solvent under reduced pressure, water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give a pale brown viscous oil (0.20 g).

This residue was dissolved in chloroform (30 ml) and manganese dioxide (0.27 g) was added thereto. After stirring the resultant mixture at 50°C overnight, additional manganese dioxide (0.19 g) was added thereto followed by stirring for 6 hr. Then the manganese dioxide was filtered off and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol system) to give a free compound (0.09 g) of the title compound as a pale brown viscous oil, which was then converted into an oxalate in a conventional manner.

m.p.: 213.1 - 214.5°C (decomp.).

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 2.06-2.23(4H,m), 2.81-3.09(6H,m), 3.41-3.47(6H,m), 3.52(2H,s), 3.67-3.75(1H,m), 4.49-4.57(1H,m), 6.43(1H,d,J=3.2Hz), 6.95(1H,d,J=8.4Hz), 7.17(2H,br-t), 7.32-7.36(2H,m), 7.41-7.46(3H,m), 7.72(1H,d,J=8.4Hz).

ESI-Mass ; 454(MH+).

Example 305: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-carbamoylmethylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carboxymethyl-indoline (0.22 g) obtained in Example 146 was dissolved in N,N-dimethylformamide (5 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.11 g) and the resultant mixture was stirred under nitrogen atmosphere at room temperature for 15 min. Next, a saturated solution (2 ml) of ammonia in methanol was added thereto and the mixture was further stirred overnight. After evaporating the solvent under reduced pressure, water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give a pale brown viscous oil (0.11 g).

This residue was dissolved in chloroform (30 ml) and manganese dioxide (0.24 g) was added thereto. After stirring the resultant mixture at 50°C for 4 hr, additional manganese dioxide (0.12 g) was added thereto followed by stirring overnight. Then the manganese dioxide was filtered off and the solvent was evaporated under reduced pressure. The residue was recrystallized from chloroform/n-hexane to give the title compound (0.08 g) as a pale yellow powder.

m.p.: 159.1 - 160.8°C.

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 2.07-2.13(4H,m), 2.25-2.31(2H,m), 2.64-2.68(2H,m), 2.81-2.85(2H,m), 3.18(2H,br-d), 3.73(2H,s), 4.21-4.29(1H,m), 5.33(1H,br-s), 4.43(1H,br-s), 6.52(1H,dd, $J=3.2\text{Hz}$), 6.97-7.01(3H,m), 7.17-7.20(2H,m), 7.26(1H,d, $J=3.2\text{Hz}$), 7.29(1H,s), 7.62(1H,d, $J=8.0\text{Hz}$).
ESI-Mass ; 380(MH+).

Example 306: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(carbamoylmethyl)carbamoylmethylindole oxalate

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carboxymethyl-indoline (0.22 g) obtained in Example 146 was dissolved in N,N-dimethylformamide (5 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.11 g) and the resultant mixture was stirred under nitrogen atmosphere at room temperature for 15 min. Next, a suspension of glycineamide hydrochloride (0.31 g) and triethylamine (395 μl) in N,N-dimethylformamide (10 ml) was added thereto and the mixture was further stirred overnight. After evaporating the solvent under reduced pressure, water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give a pale brown viscous oil (0.10 g).

This residue was dissolved in chloroform (30 ml) and manganese dioxide (0.14 g) was added thereto. After stirring

the resultant mixture at 50°C overnight, additional manganese dioxide (0.10 g) was added thereto followed by stirring for 3.5 hr. Then the manganese dioxide was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography

(chloroform/methanol system) to give a free compound (0.06 g) of the title compound as a pale brown amorphous substance, which was then converted into an oxalate in a conventional manner.

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 2.06-2.22(4H,m), 2.86-3.07(6H,m), 3.57(2H,s), 3.65(2H,d,J=5.6Hz), 4.56(1H,br-s), 7.44(1H,d,J=2.8Hz), 6.96(1H,d,J=7.8Hz), 7.04(1H,br-s), 7.17(1H,br-t), 7.33-7.36(3H,m), 7.41(1H,br-s), 7.46(1H,d,J=7.8Hz), 7.50(1H,s), 8.13(1H,br-t).

ESI-Mass ; 437(MH+).

Example 307: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-dimethylaminoethyl)carbamoylmethylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (0.22 g) obtained in Example 146 was dissolved in N,N-dimethylformamide (5 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.11 g) and the resultant mixture was stirred under nitrogen atmosphere at room temperature for 15 min. Next, N,N-dimethylethylenediamine (310 ml) was added thereto and the mixture was further stirred overnight. After evaporating the solvent under reduced

pressure, water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was distilled off under reduced pressure to give a pale brown viscous oil (0.18 g).

This residue was dissolved in chloroform (30 ml) and manganese dioxide (0.24 g) was added thereto. After stirring the resultant mixture at 50 °C for 9 hr, additional manganese dioxide (0.28 g) was added thereto followed by stirring overnight. Then the manganese dioxide was filtered off and the solvent was evaporated under reduced pressure. The residue was recrystallized from chloroform/n-hexane to give the title compound (0.12 g) as a pale brown powder.

m.p.: 111.8 - 112.9°C.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.07-2.14(4H,m), 2.13(6H,s), 2.24-2.32(2H,m), 2.32(2H,t,J=6.0Hz), 2.64-2.68(2H,m), 2.81-2.85(2H,m), 3.18(2H,br-d), 3.28(2H,dt,J=6.0,6.0Hz), 3.69(2H,s), 4.21-4.29(1H,m), 5.98(1H,br-t), 6.51(1H,d,J=3.4Hz), 6.97-7.01(3H,m), 7.17-7.20(2H,m), 7.24(1H,d,J=3.4Hz), 7.30(1H,s), 7.59(1H,d,J=8.0Hz).

ESI-Mass ; 451(MH+).

Example 308: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-cyanomethylcarbamoylmethylindole oxalate

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-

carboxymethylindoline (0.22 g) obtained in Example 146 was dissolved in N,N-dimethylformamide (5 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.11 g) and the resultant mixture was stirred under nitrogen atmosphere at room temperature for 15 min. Next, aminoacetonitrile hydrochloride (0.26 g) dissolved in N,N-dimethylformamide (10 ml) was added thereto. After further adding triethylamine (394 ml), the resultant mixture was stirred overnight. After evaporating the solvent under reduced pressure, water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give a pale brown viscous oil (0.17 g).

This residue was dissolved in chloroform (30 ml) and manganese dioxide (0.25 g) was added thereto. After stirring the resultant mixture at 50°C 8 hr, additional manganese dioxide (0.28 g) was added thereto followed by stirring overnight. Then the manganese dioxide was filtered off and the solvent was evaporated under reduced pressure. The residue was purified successively by silica gel column chromatography (chloroform/methanol system) and NH silica gel column chromatography (chloroform/ethyl acetate system) to give a free compound (0.04 g) of the title compound as a pale brown viscous oil, which was then converted into an oxalate in a conventional

manner.

$^1\text{H-NMR}$ (400MHz, DMSO- d_6) ; δ (ppm) 2.04-2.21(4H,m), 2.77-3.06(6H,m), 3.41-3.46(2H,m), 3.58(2H,s), 4.13(2H,d, $J=5.6\text{Hz}$), 4.53(1H,br-s), 6.45(1H,d, $J=3.2\text{Hz}$), 6.94(1H,d, $J=8.6\text{Hz}$), 7.16(2H,br-t), 7.32-7.36(2H,m), 7.44(2H,br-s), 7.48(1H,d, $J=8.6\text{Hz}$), 8.69(1H,br-t).

ESI-Mass ; 419(MH+).

Example 309: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-methoxyethyl)carbamoylmethylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (0.22 g) obtained in Example 146 was dissolved in N,N-dimethylformamide (5 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.11 g) and the resultant mixture was stirred under nitrogen atmosphere at room temperature for 15 min. Next, 2-methoxyethylamine (245 ml) was added thereto and the mixture was further stirred for 4 hr. After evaporating the solvent under reduced pressure, water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give a pale brown viscous oil (0.19 g).

This residue was dissolved in chloroform (30 ml) and manganese dioxide (0.31 g) was added thereto. After stirring

the resultant mixture at 50°C overnight, additional manganese dioxide (0.27 g) was added thereto followed by stirring for 5 hr. Then manganese dioxide (0.19 g) was further added thereto and the resultant mixture was stirred for additional 1 hr. Then the manganese dioxide was filtered off and the solvent was evaporated under reduced pressure. The residue was recrystallized from chloroform/n-hexane to give the title compound (0.13 g) as a colorless powder.

m.p.: 113.2 - 114.4°C.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.07-2.13(4H,m), 2.25-2.31(2H,m), 2.64-2.68(2H,m), 2.81-2.85(2H,m), 3.18(2H,br-d), 3.26(3H,s), 3.39(4H,br-d), 3.71(2H,s), 4.21-4.29(1H,m), 5.81(1H,br-s), 6.52(1H,d,J=3.4Hz), 6.96-7.01(3H,m), 7.17-7.21(2H,m), 7.26(1H,d,J=3.4Hz), 7.28(1H,s), 7.60(1H,d,J=8.0Hz).

ESI-Mass ; 438(MH+).

Example 310: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-fluoroethyl)carbamoylmethylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (0.22 g) obtained in Example 146 was dissolved in N,N-dimethylformamide (5 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.11 g) and the resultant mixture was stirred under nitrogen atmosphere at room temperature for 15 min. Next, 2-fluoroethylamine

hydrochloride (0.30 g) dissolved in N,N-dimethylformamide (5 ml) was added thereto. After further adding triethylamine (397 ml), the mixture was stirred for 4 hr. After evaporating the solvent under reduced pressure, water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give pale brown crystals (0.19 g).

These crystals were dissolved in chloroform (30 ml) and manganese dioxide (0.30 g) was added thereto. After stirring the resultant mixture at 50°C overnight, additional manganese dioxide (0.26 g) was added thereto followed by stirring for 5 hr. Then manganese oxide (0.19 g) was furthermore added and the resultant mixture was stirred for additional 2 hr. Next, the manganese dioxide was filtered off and the solvent was evaporated under reduced pressure. The residue was recrystallized from chloroform/n-hexane to give the title compound (0.15 g) as a colorless powder.

m.p.: 163.3 - 163.8°C.

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 2.05-2.13(4H,m), 2.25-2.31(2H,m), 2.64-2.68(2H,m), 2.81-2.85(2H,m), 3.18(2H,br-d), 3.50(2H,ddt, $J=4.8, 28.0, 4.8\text{Hz}$), 3.74(2H,s), 4.21-4.29(1H,m), 4.43(2H,dt, $J=47.2, 4.8\text{Hz}$), 5.80(1H,br-t), 6.53(1H,d, $J=3.2\text{Hz}$), 6.97-7.01(3H,m), 7.17-7.20(2H,m), 7.26-7.28(2H,m),

7.62(1H,d,J=8.0Hz).

ESI-Mass ; 426(MH+).

Example 311: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[2-(ethylcarbamoyl)ethyl]indole oxalate

311-1) 1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-[2-(ethoxycarbonyl)vinyl]indole

55 % oily sodium hydride (0.46 g) was washed with n-hexane and suspended in tetrahydrofuran (1 ml) followed by stirring under ice-cooling. Then ethyl diethylphosphonoacetate (2.37 g) dissolved in tetrahydrofuran (7 ml) was added thereto and the resultant mixture was stirred at room temperature for 30 min. Next, 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-formylindole (3.53 g) obtained in Example 130 dissolved in tetrahydrofuran (10 ml) was added thereto and the resultant mixture was stirred under nitrogen atmosphere at room temperature for 2 days. After evaporating the solvent under reduced pressure, water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate/n-hexane system) to give the title compound (3.59 g) as yellow crystals.

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 1.36(3H,t,J=7.2Hz), 2.08-

2.14(4H,m), 2.26-2.33(2H,m), 2.65-2.69(2H,m), 2.81-
2.85(2H,m), 3.20(2H,br-d), 4.28(2H,q,J=7.2Hz), 4.23-
4.32(1H,m), 6.47(1H,d,J=16.0Hz), 6.53(1H,d,J=3.2Hz), 6.97-
7.02(2H,m), 7.17-7.21(2H,m), 7.32(1H,d,J=3.2Hz),
7.34(1H,d,J=8.4Hz), 7.52(1H,s), 7.61(1H,d,J=8.4Hz),
7.84(1H,d,J=16.0Hz).

311-2) 1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-[2-(ethoxy-carbonyl)ethyl]indole

The above 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[2-(ethoxycarbonyl)vinyl]indole (1.89 g) was dissolved in a mixture of ethanol (40 ml) and ethyl acetate (20 ml). Then 10 % Pd/C (0.10 g) was added thereto and catalytic reduction was carried out under atmospheric pressure overnight. After filtering off the catalyst, the solvent was evaporated under reduced pressure to give the title compound (1.87 g) as a colorless viscous oil.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 1.25(3H,t,J=7.2Hz), 2.06-2.12(4H,m), 2.24-2.31(2H,m), 2.64-2.70(4H,m), 2.81-2.85(2H,m), 3.08(2H,t,J=8.0Hz), 3.18(2H,br-d), 4.14(2H,q,J=7.2Hz), 4.19-4.27(1H,m), 6.48(1H,d,J=3.2Hz), 6.95-7.01(3H,m), 7.17-7.20(4H,m), 7.54(1H,d,J=8.0Hz).

311-3) 1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-(2-carboxyethyl)indole

The above 1-[1-(4-fluorophenethyl)piperidin-4-yl]-

6-[2-(ethoxycarbonyl)ethyl]indole (1.85 g) was dissolved in methanol (25 ml). Then a 5 N aqueous solution (1.75 ml) of sodium hydroxide was added thereto and the resultant mixture was stirred at room temperature overnight. After removing the solvent under reduced pressure, the residue was neutralized with 5 N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed successively with water and brine and dried over magnesium sulfate. After evaporating the solvent under reduced pressure, the title compound (1.70 g) was obtained as a pale brown amorphous substance.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 1.79-1.82(2H,m), 2.32-2.43(4H,m), 2.78-2.84(4H,m), 2.92-2.97(2H,m), 3.13(2H,t,J=7.4Hz), 3.20(2H,br-d), 4.14-4.22(1H,m), 6.40(1H,d,J=3.2Hz), 6.96-7.03(3H,m), 7.05(1H,d,J=3.2Hz), 7.16-7.20(2H,m), 7.33(1H,s), 7.49(1H,d,J=8.0Hz).

311-4) 1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-(2-ethylcarbamoyl)ethylindole oxalate

The above 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-carboxyethyl)indole (0.10 g) was dissolved in N,N-dimethylformamide (2 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.05 g) and the resultant mixture was stirred under nitrogen atmosphere at room temperature for 15 min. Next, a 70 % aqueous solution (106 ml) of ethylamine was added thereto and the mixture was stirred overnight. After

evaporating the solvent under reduced pressure, water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure and the residue was purified by NH-silica gel column chromatography (ethyl acetate/n-hexane system) to give a free compound (0.05 g) of the title compound as a colorless viscous oil, which was then converted into an oxalate in a conventional manner.

$^1\text{H-NMR}$ (400MHz, DMSO- d_6) ; δ (ppm) 2.05(2H, br-d), 2.13-2.22(2H, m), 2.39(2H, t, $J=7.8\text{Hz}$), 2.81(2H, br-t), 2.89-2.95(4H, m), 3.01-3.09(4H, m), 3.42(2H, br-d), 4.48-4.56(1H, m), 6.41(1H, d, $J=3.2\text{Hz}$), 6.89(1H, d, $J=8.0\text{Hz}$), 7.16(2H, br-t), 7.32-7.37(3H, m), 7.39(1H, d, $J=3.2\text{Hz}$), 7.43(1H, d, $J=8.0\text{Hz}$), 7.82(1H, t, $J=5.4\text{Hz}$).

ESI-Mass ; 422(MH+).

Example 312: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[2-(pyrrolidin-1-yl)ethyl]carbamoylmethylindole oxalate

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (0.21 g) obtained in Example 146 was dissolved in N,N-dimethylformamide (5 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.11 g) and the resultant mixture was stirred under nitrogen atmosphere at room

temperature for 15 min. Next, 1-(2-aminoethyl)pyrrolidine (353 ml) was added thereto and the mixture was stirred for additional 4.5 hr. After evaporating the solvent under reduced pressure, water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give a pale brown viscous oil (0.19 g).

This residue was dissolved in chloroform (30 ml) and manganese dioxide (0.17 g) was added thereto. After stirring the resultant mixture at 50°C overnight, additional manganese dioxide (0.17 g) was added thereto followed by stirring for 7 hr. Then manganese oxide (0.17 g) was furthermore added and the resultant mixture was stirred for additional 5 hr. Next, the manganese dioxide was filtered off and the solvent was removed under reduced pressure to give a free compound (0.19 g) of the title compound as a pale brown viscous oil, which was then converted into an oxalate in a conventional manner.

$^1\text{H-NMR}$ (400MHz,DMSO- d_6) ; δ (ppm) 1.78-1.82(4H,m),
1.95(2H,br-d), 2.06-2.16(2H,m), 2.41(2H,br-t), 2.70-
2.74(2H,m), 2.81-2.85(2H,m), 2.93-2.98(6H,m), 3.20(2H,br-d),
3.28-3.34(2H,m), 3.50(2H,s), 4.32-4.40(1H,m),
6.40(1H,d,J=3.2Hz), 6.94(1H,d,J=9.2Hz), 7.12(2H,br-t),
7.28-7.32(2H,m), 7.42-7.45(3H,m), 8.30(1H,br-t).

ESI-Mass ; 477(MH+).

Example 313: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[2-(morpholin-4-yl)ethyl]carbamoylmethylindole oxalate

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (0.22 g) obtained in Example 146 was dissolved in N,N-dimethylformamide (5 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.11 g) and the resultant mixture was stirred under nitrogen atmosphere at room temperature for 15 min. Next, 4-(2-aminoethyl)morpholine (379 ml) was added thereto and the mixture was stirred for additional 4 hr. After evaporating the solvent under reduced pressure, water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give a pale brown viscous oil (0.19 g).

This residue was dissolved in chloroform (30 ml) and manganese dioxide (0.17 g) was added thereto. After stirring the resultant mixture at 50°C overnight, additional manganese dioxide (0.17 g) was added thereto followed by stirring for 8 hr. Then manganese oxide (0.17 g) was furthermore added and the resultant mixture was stirred for additional 3 hr. Then manganese dioxide (0.08) g was further added and the mixture

was stirred for 1.5 hr. Then manganese dioxide (0.08) g was furthermore added and the mixture was stirred for additional 5 hr. Next, the manganese dioxide was filtered off and the solvent was distilled off under reduced pressure to give a free compound (0.20 g) of the title compound as a pale brown viscous oil, which was then converted into an oxalate in a conventional manner.

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 2.04(2H,br-d), 2.17-2.27(4H,m), 2.40-2.44(6H,m), 2.79(2H,br-t), 2.91-2.95(2H,m), 2.98-3.03(2H,m), 3.19(2H,br-q), 3.42(2H,br-d), 3.50(2H,s), 3.53(4H,br-t), 4.47-4.55(1H,m), 6.43(1H,d,J=3.2Hz), 6.96(1H,dd,J=0.8,8.0Hz), 7.13-7.18(2H,m), 7.32-7.35(2H,m), 7.42(1H,d,J=3.2Hz), 7.45-7.47(2H,m), 7.93(1H,t,J=5.6Hz).
ESI-Mass ; 493(MH+).

Example 314: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(pyridin-4-yl)methylcarbamoylmethylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (0.21 g) obtained in Example 146 was dissolved in N,N-dimethylformamide (5 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.11 g) and the resultant mixture was stirred under nitrogen atmosphere at room temperature for 15 min. Next, 4-aminomethylpyridine (283 ml) was added thereto and the mixture was stirred for additional 6 hr. After evaporating the solvent under reduced pressure,

water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give a pale brown viscous oil (0.20 g).

This residue was dissolved in chloroform (30 ml) and manganese dioxide (0.37 g) was added thereto. After stirring the resultant mixture at 50°C overnight, additional manganese dioxide (0.18 g) was added thereto followed by stirring for 3 hr. Next, the manganese dioxide was filtered off and the solvent was evaporated under reduced pressure to give the title compound (0.16 g) as a pale yellow amorphous solid.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.07-2.16(4H,m), 2.24-2.31(2H,m), 2.64-2.68(2H,m), 2.81-2.85(2H,m), 3.18(2H,br-d), 3.81(2H,s), 4.19-4.27(1H,m), 4.39(2H,d,J=6.0Hz), 5.89(1H,t,J=6.0Hz), 6.53(1H,d,J=3.2Hz), 6.97-7.01(3H,m), 7.06(2H,d,J=5.8Hz), 7.17-7.20(2H,m), 7.27(1H,d,J=3.2Hz), 7.29(1H,s), 7.63(1H,d,J=8.0Hz), 8.48(2H,d,J=5.8Hz).

ESI-Mass ; 471(MH+).

Example 315: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[2-(pyridin-2-yl)ethyl]carbamoylmethylindole oxalate

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carboxymethyl-indoline (0.23 g) obtained in Example 146 was

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dissolved in N,N-dimethylformamide (5 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.11 g) and the resultant mixture was stirred under nitrogen atmosphere at room temperature for 15 min. Next, 2-(2-aminoethyl)pyridine (352 ml) was added thereto and the mixture was stirred for additional 6 hr. After evaporating the solvent under reduced pressure, water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give a pale brown viscous oil (0.23 g).

This residue was dissolved in chloroform (30 ml) and manganese dioxide (0.42 g) was added thereto. After stirring the resultant mixture at 50°C overnight, additional manganese dioxide (0.21 g) was added thereto followed by stirring for 7.5 hr. Next, the manganese dioxide was filtered off and the solvent was evaporated under reduced pressure to give a free compound (0.23 g) of the title compound as a pale brown viscous oil, which was then converted into an oxalate in a conventional manner.

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 2.08(2H, br-d), 2.23-2.34(2H, m), 2.06(2H, t, $J=7.2\text{Hz}$), 2.93-3.00(4H, m), 3.11-3.15(2H, m), 3.41(2H, br-q), 3.48(2H, s), 3.52(2H, br-d), 4.54-4.62(1H, m), 6.44(1H, d, $J=3.0\text{Hz}$), 6.91(1H, d, $J=9.2\text{Hz}$), 7.15-7.20(4H, m),

7.33-7.36(2H,m), 7.42(1H,d,J=3.0Hz), 7.44-7.46(2H,m),
7.61(1H,dt,J=2.0,8.6Hz), 8.07(1H,t,J=5.6Hz), 8.44(1H,br-d).
ESI-Mass ; 485(MH+).

Example 316: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methylcarbamoylmethylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (0.29 g) obtained in Example 146 was dissolved in N,N-dimethylformamide (5 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.15 g) and the resultant mixture was stirred under nitrogen atmosphere at room temperature for 15 min. Next, a 40 % aqueous solution (662 ml) of methylamine was added thereto and the mixture was stirred overnight. After evaporating the solvent under reduced pressure, water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give pale brown crystals (0.22 g).

These crystals were dissolved in chloroform (30 ml) and manganese dioxide (0.49 g) was added thereto. After stirring the resultant mixture at 50°C overnight, additional manganese dioxide (0.24 g) was added thereto followed by stirring for 2 hr. Then manganese dioxide (0.19 g) was further added and the resultant mixture was stirred for 2 hr. Next, the manganese

dioxide was filtered off and the solvent was evaporated under reduced pressure. The residue was recrystallized from chloroform/n-hexane to give the title compound (0.18 g) as a pale brown powder.

m.p.: 149.4 - 150.5°C.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.05-2.13(4H,m), 2.25-2.31(2H,m), 2.64-2.68(2H,m), 2.73(3H,d,J=4.8Hz), 2.81-2.85(2H,m), 3.18(2H,br-d), 3.72(2H,s), 4.20-4.28(1H,m), 5.40(1H,br-s), 6.53(1H,d,J=3.2Hz), 6.95-7.01(3H,m), 7.17-7.20(2H,m), 7.26-7.27(2H,m), 7.61(1H,d,J=7.6Hz).

ESI-Mass ; 394(MH+).

Example 317: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-methoxypyridin-5-ylcarbonyl)indole oxalate

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-[(2-methoxypyridin-5-yl)hydroxymethyl]indoline (0.16 g) obtained in Example 189 was dissolved in chloroform (30 ml). To the resultant solution was added manganese dioxide (0.30 g) and the resultant mixture was stirred at 50°C overnight. Next, the manganese dioxide was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane system) to give a free compound (0.07 g) of the title compound as a pale brown viscous oil, which was then converted into an oxalate in a conventional manner.

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 2.04-2.11(2H,m), 2.16-2.25(2H,m), 2.75(2H,br-t), 2.89-2.97(4H,m), 3.98(3H,s), 4.68-4.76(1H,m), 6.65(1H,d,J=3.2Hz), 7.00(1H,d,J=8.8Hz), 7.15(2H,br-t), 7.31-7.34(2H,m), 7.44(1H,d,J=8.4Hz), 7.70(1H,d,J=8.4Hz), 7.80(1H,d,J=3.2Hz), 8.07(1H,s), 8.11(1H,dd,J=2.4,8.8Hz), 8.60(1H,d,J=2.4Hz).

ESI-Mass ; 458(MH+).

Example 318: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[(2-methoxypyridin-5-yl)hydroxymethyl]indole oxalate

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-(2-methoxypyridin-5-ylcarbonyl)indole (0.07 g) obtained in Example 317 was dissolved in methanol (10 ml). To the resultant solution was added sodium borohydride in portions. After confirming the disappearance of the starting compound by thin layer chromatography, the solvent was evaporated under reduced pressure. Then water was added to the residue followed by extraction with ethyl acetate. The organic layer was washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give a free compound (0.11 g) of the title compound as a colorless viscous oil, which was then converted into an oxalate in a conventional manner.

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 2.03-2.08(2H,m), 2.13-

2.21(2H,m), 2.75-3.00(6H,m), 3.40(2H,br-d), 3.80(2H,s),
4.52-4.60(1H,m), 6.42(1H,d,J=3.2Hz), 6.72(1H,d,J=8.6Hz),
6.96(1H,d,J=8.6Hz), 7.16(2H,br-t), 7.32-7.35(2H,m), 7.44-
7.46(2H,m), 7.62(1H,dd,J=2.2,8.6Hz), 7.65(1H,s),
8.19(1H,d,J=2.2Hz).

ESI-Mass ; 460(MH+).

Example 319: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1-hydroxypropyl)indole oxalate

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-formylindoline (0.10 g) obtained in Example 130 was dissolved in tetrahydrofuran (5 ml) and stirred under ice cooling. To the resultant solution was added a 1.0 M solution (0.5 ml) of ethylmagnesium bromide in tetrahydrofuran and the resultant mixture was stirred for 25 min. Next, a 1.0 M solution (0.5 ml) of ethyl magnesium bromide in tetrahydrofuran was further added thereto and the resultant mixture was stirred for additional 15 min. To the reaction mixtures were successively added a saturated aqueous solution of ammonium chloride, water and ethyl acetate. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give a free compound (0.10 g) of the title compound as a pale brown viscous oil, which was then converted into an oxalate in a conventional manner.

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 0.85(3H,t,J=7.4Hz), 1.62-1.75(2H,m), 2.08(2H,br-d), 2.19-2.29(2H,m), 2.93-2.99(4H,m), 3.08-3.12(2H,m), 3.49(2H,br-d), 4.54(1H,t,J=6.4Hz), 4.59-4.65(1H,m), 6.43(1H,d,J=3.0Hz), 7.00(1H,d,J=8.0Hz), 7.17(2H,br-t), 7.33-7.36(2H,m), 7.41(1H,d,J=3.0Hz), 7.47(1H,d,J=8.0Hz), 7.49(1H,s).

ESI-Mass ; 381(MH+).

Example 320: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1-hydroxy-1-methylethyl)indoline

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-(1-hydroxy-1-methylethyl)indoline (0.1 g) obtained in Example 139 and activated manganese dioxide (0.5 g) were treated as in Example 288 to give the title compound (0.07 g) as a pale yellow oil (yield: 70.3 %).

Next, this product was converted into an oxalate in a conventional manner.

Oxalate:

m.p.: 97 - 99°C.

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 1.49(6H,s), 2.04-2.15(2H,m), 2.16-2.30(2H,m), 2.92-3.06(4H,m), 3.08-3.19(2H,m), 3.47-3.56(2H,m), 4.58-4.68(1H,m), 6.42(1H,d,J=3.2Hz), 7.13(1H,dd,J=8.4,1.2Hz), 7.13-7.21(2H,m), 7.32-7.37(2H,m), 7.40(1H,d,J=3.2Hz), 7.50(1H,d,J=8.4Hz), 7.63(2H,br-s).

FAB-Mass ; 381(MH+).

Example 321: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(3-hydroxypropyl)indole

A solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-formylindole (0.20 g) obtained in Example 130 in tetrahydrofuran (2 ml) was added dropwise at room temperature into a solution prepared by adding triethyl phosphonoacetate (0.14 g) to a suspension of sodium hydride (0.03 g) in tetrahydrofuran (5 ml). After 1 hr, a saturated aqueous solution (10 ml) of ammonium chloride was added thereto and the mixture was extracted with ethyl acetate. The extract was washed successively with water and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was dissolved in ethanol (10 ml) and then hydrogenated in the presence of 10 % palladium carbon (0.05 g) at ordinary temperature under atmospheric pressure. After 2 hr, the reaction mixture were filtered and the filtrate was concentrated. The residue was dissolved in tetrahydrofuran (3 ml) and the resulting solution was added dropwise into a suspension of lithium aluminum hydride (0.03 g) in tetrahydrofuran (5 ml). After stirring the reaction mixtures at room temperature for 1 hr, water (0.03 ml), 5 N sodium hydroxide (0.09 ml) and further water (0.03 ml) were added thereto in this order. The resulting precipitate was filtered off. After washing with ethyl acetate, the filtrate was

concentrated. The residue was purified by silica gel column chromatography (dichloromethane/methanol system) to give the title compound (0.05 g) as a pale yellow powder (yield: 23 %). m.p.: 131 - 133°C.

$^1\text{H-NMR}$ (400MHz, DMSO- d_6) ; δ (ppm) 1.90-2.05(4H,m), 2.20-2.29(2H,m), 2.55-2.62(2H,m), 2.74-2.81(2H,m), 2.81(3H,s), 3.06-3.13(2H,m), 4.25(2H,d, J=6.4Hz), 4.26-4.38(1H,m), 6.42(1H,d, J=3.2Hz), 7.02(1H,dd, J=8.0, 1.2Hz), 7.08-7.14(2H,m), 7.27-7.33(2H,m), 7.47-7.53(3H,m).

ESI-Mass ; 381(MH+).

Example 322: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methanesulfonamidomethylindole
322-1) 1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-formylindole

A suspension of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-formylindoline (3.60 g) obtained in Example 130 and activated manganese dioxide (15.0 g) in chloroform (100 ml) was heated under reflux for 6 hr under vigorous stirring. Then the reaction mixtures were filtered through celite and the residue was washed with chloroform. After concentrating the filtrate under reduced pressure, the residue was recrystallized from ethyl acetate/hexane to give the title compound (2.45 g) as a yellow powder (yield: 68.4 %).

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 2.09-2.42(6H,m), 2.67-

2.75(2H,m), 2.83-2.91(2H,m), 3.19-3.28(2H,br-d), 4.35-4.45(1H,m), 6.61(1H,d,J=3.2Hz), 6.95-7.05(2H,m), 7.16-7.23(2H,m), 7.48(1H,d,J=3.2Hz), 7.62(1H,dd,J=8.0,1.2Hz), 7.72(1H,d,J=8.0Hz), 7.98(1H,s), 10.07(1H,s).

322-2) 1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-hydroxyiminomethylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-formylindole (3.78 g), hydroxylamine hydrochloride (0.90 g) and anhydrous sodium acetate (1.06 g) were stirred in ethanol (60 ml) at room temperature for 2 hr. Then the liquid reaction mixture was concentrated and the residue was partitioned between ethyl acetate (150 ml) and a 1 N aqueous solution (30 ml) of sodium hydroxide. The ethyl acetate layer was washed successively with water and brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from ether/hexane and the crystals were collected by filtration, washed with hexane and dried to give the title compound (3.60 g) as a pale yellow powder (yield: 91.3 %).

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.03-37(6H,m), 2.61-2.74(2H,m), 2.81-2.91(2H,m), 3.15-3.27(2H,m), 4.20-4.32(1H,m), 6.51(0.5H,d,J=3.2Hz), 6.68(0.5H,d,J=3.2Hz), 6.95-7.02(2H,m), 7.14-7.22(2H,m), 7.31(0.5H,d,J=3.2Hz), 7.32(0.5H,dd,J=8.0,1.2Hz), 7.38(0.5H,dd,J=8.0,1.2Hz), 7.45(0.5H,d,J=3.2Hz), 7.58-7.63(1H,m), 7.66(0.5H,d,J=8.0Hz),

7.74(0.5H,br-s), 8.32(0.5H,s).

322-3) 1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-aminomethylindole

Into a suspension of aluminum lithium hydride (1.0 g) in tetrahydrofuran (100 ml) was added dropwise at room temperature a solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-hydroxyiminomethylindole (3.60 g) in tetrahydrofuran (50 ml) under ice cooling and stirring, and the resultant mixture was heated under reflux for 3 hr. Under cooling with ice water, water (1 ml), a 5 N aqueous solution (3 ml) of sodium hydroxide and further water (1 ml) were carefully added dropwise into the reaction mixtures in this order followed by vigorous stirring. The resulting precipitate was filtered off and the filtrate was concentrated under reduced pressure. Then the residue was purified by NH silica gel column chromatography (ethyl acetate) to give the title compound (2.56 g) as a pale yellow powder (yield: 73.9 %).

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 1.86-2.18(4H,m), 2.22-2.32(2H,m), 2.61-2.70(2H,m), 2.78-2.87(2H,m), 3.10-3.18(2H,m), 4.05(2H,d,J=4.2Hz), 4.20-4.28(1H,m), 6.46(1H,d,J=3.2Hz), 6.95-7.03(2H,m), 7.05(1H,dd,J=8.4,1.6Hz), 7.14-7.19(2H,m), 7.21(1H,d,J=3.2Hz), 7.50-7.53(1H,m), 7.53(1H,d,J=8.4Hz).

322-4) 1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-

methanesulfonamidomethylindole

Into a solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminomethylindoline (0.12 g) obtained in the above Example and triethylamine (0.5 g) in ethyl acetate (15 ml) was added dropwise under ice cooling methanesulfonyl chloride (0.08 ml) and the resultant mixture was stirred at room temperature for 1 hr. After adding a 1 N aqueous solution (2 ml) of sodium hydroxide and water (15 ml), the reaction mixtures were extracted with ethyl acetate. The ethyl acetate layer was washed successively with water and brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was crystallized from ether/hexane and the crystals were collected by filtration, washed with hexane and dried to give the title compound (0.11 g) as a white powder (yield: 75 %). m.p.: 121 - 122°C.

$^1\text{H-NMR}$ (400MHz,DMSO- d_6) ; δ (ppm) 1.90-2.05(4H,m), 2.20-2.29(2H,m), 2.55-2.62(2H,m), 2.74-2.81(2H,m), 2.81(3H,s), 3.06-3.13(2H,m), 4.25(2H,d,J=6.4Hz), 4.26-4.38(1H,m), 6.42(1H,d,J=3.2Hz), 7.02(1H,dd,J=8.0,1.2Hz), 7.08-7.14(2H,m), 7.27-7.33(2H,m), 7.47-7.53(3H,m).

ESI-Mass ; 430(MH+).

Example 323: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-isopropylsulfonamidomethylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-

aminomethylindoline (0.20 g), triethylamine (0.3 ml) and isopropylsulfonyl chloride (0.1 ml) were treated as in Example 322-4) to give the title compound (0.06 g) as a white powder (yield: 23 %).

m.p.: 90 - 92 °C.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 1.38(6H,d,J=7.2Hz), 2.05-2.18(4H,m), 2.22-2.36(2H,m), 2.60-2.75(2H,m), 2.79-2.90(2H,m), 3.05-3.25(3H,m), 4.20-4.35(1H,m), 4.35-4.50(3H,m), 6.52(1H,d,J=3.2Hz), 6.99(2H,t,J=8.8Hz), 7.05(1H,d,J=8.0Hz), 7.19(2H,dd,J=5.4,8.8Hz), 7.27(1H,d,J=3.2Hz), 7.38(1H,s), 7.60(1H,d,J=8.0Hz).

MS m/e ; 458(MH+).

Example 324: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-n-propylsulfonamidomethylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-aminomethylindoline (0.25 g), triethylamine (0.4 ml) and n-propylsulfonyl chloride (0.3 ml) were treated as in Example 322-4) to give the title compound (0.17 g) as a beige powder (yield: 53 %).

m.p.: 80 - 81°C.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 0.99(3H,t,J=7.4Hz), 1.76-1.88(2H,m), 2.02-2.20(4H,m), 2.34-2.37(2H,m), 2.60-2.74(2H,m), 2.76-3.00(4H,m), 3.12-3.28(2H,m), 4.20-4.34(1H,m), 4.43(2H,d,J=5.6Hz), 4.48(1H,br-s),

6.52(1H,d,J=3.2Hz), 6.99(2H,t,J=8.4Hz), 7.05(1H,d,J=8.0Hz),
7.19(2H,dd,J=5.8,8.4Hz), 7.28(1H,d,J=3.2Hz), 7.38(1H,s),
7.61(1H,d,J=8.0Hz).

MS m/e ; 458(MH+).

Example 325: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(3-chloropropyl)sulfonamidomethylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-aminomethylindoline (0.25 g), triethylamine (0.4 ml) and 3-chloropropylsulfonyl chloride (0.1 ml) were treated as in Example 322-4) to give the title compound (0.25 g) as a white powder (yield: 71 %).

m.p.: 143 - 145°C.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.06-2.16(4H,m), 2.19-2.36(4H,m), 2.63-2.72(2H,m), 2.79-2.88(2H,m), 3.09(2H,t,J=7.4Hz), 3.15-3.24(2H,m), 3.59(2H,t,J=6.4Hz), 4.20-4.34(1H,m), 4.44(2H,d,J=5.6Hz), 4.56(1H,br-s), 6.52(1H,d,J=3.2Hz), 6.99(2H,t,J=8.4Hz), 7.05(1H,d,J=8.4Hz), 7.19(2H,dd,J=5.6,8.4Hz), 7.28(1H,d,J=3.2Hz), 7.38(1H,s), 7.62(1H,d,J=8.4Hz).

MS m/e ; 492, 494(MH+).

Example 326: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1,3-propanesultam-2-yl)methylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-(3-

chloropropyl)sulfonamidomethylindole (144 mg) obtained in the above Example 325 was dissolved in N,N-dimethylformamide (4 ml). Then sodium hydride (40 mg, 60 - 70 % oily) was added thereto at room temperature and the resultant mixture was stirred for 20 min. After adding water, the mixture was extracted with ethyl acetate and dried over magnesium sulfate. After evaporating the solvent, the residue was purified by silica gel column chromatography (ethyl acetate) to give the title compound (110 mg) as a colorless amorphous substance (yield: 83 %).

This amorphous substance was dissolved in ethanol (5 ml) and oxalic acid (20 mg) dissolved in ethanol (1 ml) was added thereto. The resulting salt was powdered by adding ethyl acetate and collected by filtration to give an oxalate (82 mg) of the title compound as a white powder.

Oxalate:

m.p.: 171 - 172°C.

Free compound:

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 2.10-2.38(4H,m), 2.22-2.36(4H,m), 2.62-2.72(2H,m), 2.78-2.88(2H,m), 3.06-3.28(6H,m), 4.20-4.38(1H,m), 4.30(2H,s), 6.52(1H,d,J=3.2Hz), 6.99(2H,t,J=8.4Hz), 7.07(1H,d,J=8.0Hz), 7.19(2H,dd,J=5.6 and 8.4Hz), 7.27(1H,d,J=3.2Hz), 7.37(1H,s), 7.59(1H,d,J=8.0Hz).

MS m/e ; 456(MH+).

Example 327: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-propionylaminomethylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-propionylaminomethylindole (0.16 g) obtained in Example 156 and activated manganese dioxide (0.8 g) were treated as in Example 288 to give the title compound (0.12 g) as a white powder (yield: 75.3 %).

m.p.: 141 - 142°C.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 1.18(3H,t,J=7.2Hz), 2.06-2.15(2H,m), 2.51(2H,q,J=7.2Hz), 2.28-2.50(2H,m), 2.64-2.98(4H,m), 3.16-3.35(2H,m), 4.22-4.34(1H,m), 4.56(2H,d,J=6Hz), 6.51(1H,d,J=3.2Hz), 6.96-7.05(2H,m), 7.16-7.23(2H,m), 7.24(1H,d,J=3.2Hz), 7.36(1H,br-s), 7.58(1H,d,J=8.0Hz).

ESI-Mass ; 408(MH+).

Example 328: Synthesis of 3-chloro-1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindole (0.1 g) obtained in Example was reacted with 1-chlorosuccinimide (0.04 g) in benzene (10 ml) at 80°C for 1 hr. Then the liquid reaction mixture was diluted with ethyl acetate (20 ml), washed successively with water and brine, dried over magnesium sulfate and concentrated under reduced

pressure. The residue was crystallized from ether/hexane and the crystals were collected by filtration, washed with hexane and dried to give the title compound (0.04 g) as a white powder (yield: 36.8 %).

m.p.: 101 - 102°C.

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 1.95-2.15(4H,m), 2.03(3H,s), 2.20-2.50(2H,m), 2.72-3.00(4H,m), 3.28-3.40(2H,m), 4.20-4.30(1H,m), 4.54(2H,d,J=6.4Hz), 6.95-7.04(2H,m), 7.10(1H,d,J=8.0Hz), 7.17-7.24(3H,m), 7.35(1H,s), 7.55(1H,d,J=8.0Hz).

ESI-Mass ; 428(MH+).

Example 329: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(4-hydroxybutyroylamidomethyl)indole oxalate

4-Acetoxybutyric acid (0.07 g) synthesized in accordance with the method described in Tetrahedron., 45(24), 7783 - 7794, 1989. was reacted with 1,1'-carbonyldiimidazole (0.08 g) in chloroform (5 ml). Next, 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminomethylindole (0.13 g) obtained in Example 322-3) was added thereto and the resultant mixture was stirred at room temperature for 3 hr. After concentrating the reaction mixtures, a 5 N aqueous solution of sodium hydroxide (2 ml) and methanol (10 ml) were added to the residue. After reacting at 50°C for 1 hr, the solvent was concentrated under reduced pressure and the residue was

purified by silica gel column chromatography (dichloromethane/methanol system). The resulting pale yellow oil was converted into an oxalate in a conventional manner to give the oxalate (0.04 g) of the title compound as a pale brown amorphous substance (yield: 20.5 %).

Oxalate:

$^1\text{H-NMR}$ (400MHz, DMSO- d_6) ; δ (ppm) 1.68(2H,m), 2.08-2.34(4H,m), 2.18(2H,t, J=7.6Hz), 2.96-3.29(6H,m), 3.39(2H,t, J=6.8Hz), 3.56-3.66(2H,m), 4.36(2H,d, J=5.2Hz), 4.58-4.70(1H,m), 6.46(1H,d, J=3.6Hz), 6.96(1H,d, J=8.0Hz), 7.15-7.23(2H,m), 7.32-7.46(3H,m), 7.50(1H,d, J=8.0Hz), 8.26-8.33(1H,m).

ESI-Mass ; 438(MH+).

Example 330: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-hydroxyethoxyindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-hydroxyethoxyindoline (25.2 mg) obtained in Example 121 was dissolved in chloroform (5 ml). To the resultant solution was added activated manganese dioxide (138 mg). The resulting suspension was stirred at room temperature for 22 hr, then filtered through celite and washed with chloroform. The filtrate was concentrated under reduced pressure and crystallized from ethyl acetate/hexane to give the title compound (12.0 mg) as a white solid (yield: 48 %).

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 2.05-2.13(4H,m), 2.22-

2.30(2H,m), 2.64(2H,t,J=7.5Hz), 2.83(2H,t,J=7.5Hz),
3.18(2H,br-d,J=12.1Hz), 4.00(2H,t,J=4.6Hz), 4.09-4.17(1H,m),
4.17(2H,t,J=4.6Hz), 6.46(1H,d,J=3.3Hz),
6.80(1H,dd,J=8.6,2.2Hz), 6.88(1H,d,J=2.2Hz),
6.99(2H,t,J=8.4Hz), 7.15(1H,d,J=3.3Hz),
7.18(2H,dd,J=8.4,5.5Hz), 7.51(1H,d,J=8.6Hz).

m.p.: 118 - 119°C.

Mass: FAB+383(M+H)⁺.

Example 331: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methanesulfonylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-methanesulfonylindoline (19.2 mg) obtained in Example 128 was dissolved in chloroform (5 ml). To the resultant solution was added activated manganese dioxide (100 mg). The resulting suspension was stirred at room temperature for 22 hr and then at 60°C for additional 22 hr. After the completion of the reaction, the reaction mixtures were filtered through celite and washed with chloroform. The filtrate was concentrated under reduced pressure and crystallized from ethyl acetate/hexane to give the title compound (5.0 mg) as a white solid (yield: 26 %).

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.06-2.24(4H,m),
2.32(2H,td,J=11.6,2.0Hz), 2.66(2H,t,J=7.2Hz),
2.83(2H,t,J=7.2Hz), 3.19(2H,br-d,J=9.9Hz), 4.33-4.42(1H,m),

6.64(1H,d,J=3.3Hz), 6.99(2H,t,J=8.8Hz),
7.19(2H,dd,J=8.8,5.5Hz), 7.49(1H,d,J=3.3Hz),
7.61(1H,dd,J=7.3,1.1Hz), 7.77(1H,d,J=7.3Hz), 8.04(1H,br-s).
m.p.: 133 - 135°C.
Mass: FAB+401(M+H)⁺.

Example 332: Synthesis of 1-[1-(2,6-difluoro-3-pyridylethyl)piperidin-4-yl]indole

1-[1-(2,6-Difluoro-3-pyridylethyl)piperidin-4-yl]indoline (30.5 mg) obtained in Example 57 was dissolved in chloroform (5 ml). To the resultant solution was added activated manganese dioxide (185 mg). The resulting suspension was stirred at room temperature for 22 hr, filtered through celite and washed with chloroform. The filtrate was concentrated under reduced pressure to give the title compound (27.4 mg) as an oil (yield: 90 %).

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.00-2.15(4H,m),
2.28(2H,td,J=11.7,3.1Hz), 2.66(2H,t,J=8.1Hz),
2.85(2H,t,J=8.1Hz), 3.14(2H,br-d,J=11.7Hz), 4.24-4.30(1H,m),
6.52(1H,d,J=3.1Hz), 6.79(1H,dd,J=8.1,2.7Hz),
7.10(1H,t,J=7.9Hz), 7.21(1H,t,J=7.9Hz), 7.23(1H,d,J=3.1Hz),
7.37(1H,d,J=7.9Hz), 7.63(1H,d,J=7.9,5.3Hz),
7.76(1H,dd,J=17.2,8.1Hz).

Mass ; FAB+341(M+H).

Example 333: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-

4-yl]-6-fluoroindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-fluoroindoline (28.8 mg) obtained in Example 103 was dissolved in chloroform (5 ml). To the resultant solution was added activated manganese dioxide (160 mg). The resulting suspension was stirred at room temperature for 22 hr, filtered through celite and washed with chloroform. The filtrate was concentrated under reduced pressure to give the title compound (20.1 mg) as an oil (yield: 70 %).

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.04-2.15(4H,m),
2.26(2H,td,J=11.4,3.3Hz), 2.65(2H,t,J=8.8Hz),
2.82(2H,t,J=8.8Hz), 3.18(2H,br-d,J=11.4Hz), 4.08-4.17(1H,m),
6.50(1H,d,J=3.3Hz), 6.87(1H,td,J=8.8,1.6Hz),
6.99(2H,t,J=8.6Hz), 7.03(2H,dd,J=10.4,1.6Hz),
7.18(2H,dd,J=8.6,5.5Hz), 7.22(1H,d,J=3.3Hz),
7.52(1H,dd,J=8.8,5.3Hz).

Mass ; FAB : 340(M+H)+.

Example 334: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]thiazolo[5,4-f]indole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]thiazolo[5,4-f]indoline (23.7 mg) obtained in Example 234 was dissolved in chloroform (5 ml). To the resultant solution was added activated manganese dioxide (130 mg). The resulting suspension was stirred at room temperature for 22 hr. Then the

reaction mixtures were filtered through celite and washed with chloroform. The filtrate was concentrated under reduced pressure and crystallized from ethyl acetate/hexane to give the title compound (12.6 mg) as a pale yellow solid (yield: 53 %).

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 2.07-2.18(4H,m), 2.24-2.35(2H,m), 2.66(2H,t, $J=7.0\text{Hz}$), 2.83(2H,t, $J=7.0\text{Hz}$), 3.21(2H,br-d, $J=12.1\text{Hz}$), 4.36(1H,tt, $J=11.7, 4.4\text{Hz}$), 6.60(1H,d, $J=3.5\text{Hz}$), 7.00(2H,t, $J=8.6\text{Hz}$), 7.19(2H,dd, $J=8.6, 5.5\text{Hz}$), 7.49(1H,d, $J=3.5\text{Hz}$), 8.13(2H,s), 8.92(1H,s).

m.p.: 152 - 154°C.

Mass: FAB+380(M+H) $^+$.

Example 335: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(N-methylmethanesulfonylamino)indole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-(N-methylmethanesulfonylamino)indoline (34.6 mg) obtained in Example 120 was dissolved in chloroform (5 ml). To the resultant solution was added activated manganese dioxide (190 mg). The resulting suspension was stirred at room temperature for 22 hr, then filtered through celite and washed with chloroform. The filtrate was concentrated under reduced pressure and crystallized from ethyl acetate/hexane to give the title compound (24.7 mg) as a white solid (yield: 72 %).

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 2.01-2.17(4H,m),

2.28(2H,td,J=11.7,3.3Hz), 2.65(2H,t,J=8.2Hz),
2.83(2H,t,J=8.2Hz), 2.88(3H,s), 3.17(2H,br-d,J=12.1Hz),
3.39(3H,s), 4.25(1H,tt,J=11.2,5.2Hz), 6.52(1H,d,J=3.3Hz),
6.99(2H,t,J=8.6Hz), 7.04(1H,dd,J=8.4,1.8Hz),
7.19(2H,dd,J=8.6,5.5Hz), 7.30(1H,d,J=3.3Hz),
7.47(1H,d,J=1.8Hz), 7.61(1H,d,J=8.4Hz).

m.p.: 192 - 194°C.

Mass: FAB+430(M+H)⁺.

Example 336: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methanesulfonyloxyindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-methanesulfonyloxyindoline (53.4 mg) obtained in Example 122 was dissolved in chloroform (5 ml). To the resultant solution was added activated manganese dioxide (300 mg). The resulting suspension was stirred at room temperature for 22 hr. Then the reaction mixtures were filtered through celite and washed with chloroform. The filtrate was concentrated under reduced pressure and crystallized from ethyl acetate/hexane to give the title compound (40.0 mg) as a white solid (yield: 75 %).

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 1.87-2.01(4H,m),
2.22(2H,br-t,J=10.6Hz), 2.55(2H,t,J=7.9Hz),
2.75(2H,t,J=7.9Hz), 3.06(2H,br-d,J=11.2Hz), 3.34(3H,s),
4.32-4.41(1H,m), 6.50(1H,d,J=2.6Hz), 6.98(1H,dd,J=8.4,1.5Hz),
7.09(2H,t,J=9.0Hz), 7.27(2H,dd,J=9.0,5.7Hz),

7.57(1H,d,J=1.5Hz), 7.56(1H,d,J=8.4Hz), 7.60(1H,d,J=2.6Hz).

m.p.: 213 - 215°C.

Mass: FAB+417(M+H)⁺.

Example 337: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-carbamoylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carbamoylindoline (14.1 mg) obtained in Example 125 was dissolved in chloroform (5 ml). To the resultant solution was added activated manganese dioxide (80 mg). The resulting suspension was stirred at room temperature for 22 hr, then filtered through celite and washed with chloroform. The filtrate was concentrated under reduced pressure and crystallized from ethyl acetate/hexane to give the title compound (5.0 mg) as a white solid (yield: 36 %).

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.05-2.14(4H,m), 2.22-2.31(2H,m), 2.62-2.67(2H,m), 2.78-2.84(2H,m), 3.18(2H,br-d, J=10.3Hz), 4.35-4.44(1H,m), 6.57(1H,d,J=3.3Hz), 6.99(2H,t,J=8.2Hz), 7.18(2H,dd,J=8.2,5.3Hz), 7.39(1H,d,J=3.3Hz), 7.40(1H,d,J=8.1Hz), 7.64(1H,d,J=8.1Hz), 8.10(1H,br-s).

m.p.: 238 - 240°C.

Mass: FAB+366(M+H)⁺.

Example 338: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(N-methylsulfamoylmethyl)indole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-(N-methylsulfamoylmethyl)indoline (30.4 mg) obtained in Example 164 was dissolved in chloroform (5 ml). To the resultant solution was added activated manganese dioxide (165 mg). The resulting suspension was stirred at room temperature for 22 hr. Then the reaction mixtures were filtered through celite and washed with chloroform. The filtrate was concentrated under reduced pressure and crystallized from ethyl acetate/hexane to give the title compound (24 mg) as a white solid (yield: 79 %).

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 1.99-2.04(4H,m), 2.17-2.25(2H,m), 2.54(2H,d,J=4.8), 2.55(2H,t,J=8.4Hz), 2.76(2H,t,J=8.4Hz), 3.08(2H,br-d,J=11.7Hz), 4.25-4.35(1H,m), 4.37(2H,s), 6.43(1H,d,J=3.1Hz), 6.83(1H,q,J=4.8Hz), 7.01(1H,d,J=8.4Hz), 7.09(2H,t,J=8.8Hz), 7.27(2H,dd,J=8.8,5.7Hz), 7.50(1H,d,J=8.4Hz), 7.51(1H,s), 7.52(1H,d,J=3.1Hz).

m.p.: 172 - 175°C.

Mass: FAB+430(M+H)⁺.

Example 339: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-acetamidoindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-acetamidoindoline (32 mg) obtained in Example 115 was dissolved in chloroform (5 ml). To the resultant solution was added activated manganese dioxide (160 mg). The resulting

suspension was stirred at room temperature for 22 hr, then filtered through celite and washed with chloroform. The filtrate was concentrated under reduced pressure and crystallized from ethyl acetate/hexane to give the title compound (23 mg) as a pale red solid (yield: 72 %).

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 1.85-2.00(4H,m), 2.02(3H,s), 2.13-2.23(2H,m), 2.55(2H,t,J=7.7Hz), 2.75(2H,t,J=7.7Hz), 3.08(2H,br-d,J=11.7Hz), 4.07-4.18(1H,m), 6.35(1H,d,J=2.2Hz), 7.05(1H,d,J=8.6Hz), 7.09(2H,t,J=9.0Hz), 7.27(2H,dd,J=9.0,6.0Hz), 7.39(1H,d,J=2.2Hz), 7.40(1H,d,J=8.6Hz), 7.92(1H,s), 9.85(1H,br-s).

m.p.: 195 - 196°C.

Mass: FAB+380(M+H)⁺.

Example 340: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1,2-dihydroxypropan-3-yl)carbamoylmethylindole oxalate

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (0.17 g) obtained in Example 146 was dissolved in N,N-dimethylformamide (5 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.09 g) and the resultant mixture was stirred under nitrogen atmosphere at room temperature for 15 min. Next, 1-amino-2,3-propanediol (0.40 g) dissolved in N,N-dimethylformamide (1 ml) was added thereto and the mixture was stirred for additional 7.5 hr. After

evaporating the solvent under reduced pressure, water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give a pale brown viscous oil (0.14 g).

The resulting residue was dissolved in chloroform (30 ml) and manganese dioxide (0.27 g) was added thereto. After stirring the resultant mixture at 50°C overnight, additional manganese dioxide (0.13 g) was added thereto followed by stirring for 3 hr. Next, the manganese dioxide was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol system) to give a free title compound (0.07 g) as a pale brown amorphous substance, which was then converted into an oxalate in a conventional manner.

$^1\text{H-NMR}$ (400MHz,DMSO- d_6) ; δ (ppm) 2.07(2H,br-d), 2.18-2.27(2H,m), 2.84-3.06(7H,m), 3.17-3.28(3H,m), 3.45-3.53(3H,m), 3.53(2H,s), 4.50-4.58(1H,m), 6.43(1H,d,J=3.2Hz), 6.95(1H,d,J=8.8Hz), 7.16(2H,br-t), 7.32-7.36(2H,m), 7.41-7.46(3H,m), 7.99(1H,t,J=5.4Hz).

ESI-Mass ; 454(MH+).

Example 341: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(pyridin-2-yl)methylcarbamoylmethylindole oxalate

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carboxymethyl-indoline (0.21 g) obtained in Example 146 was dissolved in N,N-dimethylformamide (5 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.11 g) and the resultant mixture was stirred under nitrogen atmosphere at room temperature for 15 min. Next, 2-aminomethylpyridine (287 ml) was added thereto and the mixture was stirred for additional 4 hr. After evaporating the solvent under reduced pressure, water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give a pale brown viscous oil (0.20 g).

The resulting residue was dissolved in chloroform (30 ml) and manganese dioxide (0.36 g) was added thereto. After stirring the resultant mixture at 50°C overnight, additional manganese dioxide (0.18 g) was added thereto followed by stirring for 6 hr. Next, the manganese dioxide was filtered off and the solvent was evaporated under reduced pressure to give a free title compound (0.18 g) as a pale brown viscous oil, which was then converted into an oxalate in a conventional manner.

$^1\text{H-NMR}$ (400MHz, DMSO- d_6) ; δ (ppm) 2.09(2H, br-d), 2.25-2.34(2H, m), 2.92-3.00(4H, m), 3.09-3.17(2H, m), 3.52(2H, br-d),

3.62(2H,s), 4.37(2H,d,J=5.8Hz), 4.54-4.64(1H,m),
6.45(1H,d,J=3.4Hz), 7.01(1H,d,J=8.0Hz), 7.17(2H,br-t),
7.22-7.25(2H,m), 7.33-7.36(2H,m), 7.42(1H,d,J=1.6Hz),
7.48(1H,d,J=8.0Hz), 7.50(1H,s), 7.68-7.72(1H,m),
7.48(1H,d,J=3.4Hz), 8.63(1H,t,J=5.8Hz).

ESI-Mass ; 471(MH+).

Example 342: Synthesis of 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-methylcarbamoylmethylindole

342-1) 1-[1-(2-Fluorophenethyl)piperidin-4-yl]-6-hydroxymethylindoline

1-[1-(2-Fluorophenethyl)piperidin-4-yl]-6-formylindoline (6.85 g) obtained in Example 348-3) was dissolved in methanol (50 ml) and tetrahydrofuran (25 ml), and the resultant solution was stirred under ice cooling. Then sodium borohydride was added thereto in portions. After confirming the disappearance of the starting material by thin layer chromatography, the solvent was evaporated under reduced pressure and ethyl acetate and an 8N aqueous solution of sodium hydroxide were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give the title compound (8.10 g) as colorless crystals.

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 1.72-1.84(4H,m), 2.13-

2.19(2H,m), 2.60-2.64(2H,m), 2.84-2.88(2H,m),
2.93(2H,t,J=8.4Hz), 3.13(2H,br-d), 3.42(2H,t,J=8.4Hz),
3.38-3.46(1H,m), 4.59(2H,s), 6.44(1H,s), 6.57(1H,d,J=7.2Hz),
6.99-7.04(2H,m), 7.04-7.08(1H,m), 7.16-7.23(2H,m).

342-2) 1-[1-(2-Fluorophenethyl)piperidin-4-yl]-6-chloromethylindoline

Conc. hydrochloric acid (30 ml) was added to the 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-hydroxymethylindoline (7.49 g) obtained above and the resultant mixture was stirred at 80°C overnight. Next, it was neutralized with a 5 N aqueous solution of sodium hydroxide under ice cooling and then the pH value thereof was adjusted to about pH 10 with a 10 % aqueous solution of sodium carbonate followed by extraction with ethyl acetate. Then it was washed with brine and dried over magnesium sulfate. After evaporating the solvent under reduced pressure, the title compound (8.10 g) was obtained as pale brown crystals.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 1.72-1.85(4H,m), 2.14-2.21(2H,m), 2.60-2.65(2H,m), 2.84-2.89(2H,m),
2.93(2H,t,J=8.4Hz), 3.14(2H,br-d), 3.37-3.44(1H,m),
3.43(2H,t,J=8.4Hz), 4.52(2H,s), 6.40(1H,d,J=1.2Hz),
6.59(1H,dd,J=1.2,7.4Hz), 6.99-7.04(2H,m), 7.05-7.09(1H,m),
7.16-7.24(2H,m).

342-3) 1-[1-(2-Fluorophenethyl)piperidin-4-yl]-6-

cyanomethylindoline

Dimethyl sulfoxide (50 ml) was added to the 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-chloromethylindoline (6.51 g) obtained above. After dissolving, sodium cyanide (0.94 g) was added thereto and the resultant mixture was stirred at 50°C for 2 hr. Then ice water was added thereto followed by extraction with ethyl acetate. Next, it was washed successively with a dilute aqueous solution of sodium chloride and a saturated aqueous solution of sodium chloride and dried over magnesium sulfate. After evaporating the solvent under reduced pressure, the residue was purified by NH-silica gel column chromatography (ethyl acetate/n-hexane system) to give the title compound (4.95 g) as a pale yellow viscous oil.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 1.72-1.83(4H,m), 2.14-2.21(2H,m), 2.61(2H,m), 2.84-2.88(2H,m), 2.94(2H,t,J=8.4Hz), 3.13(2H,br-d), 3.35-3.44(1H,m), 3.44(2H,t,J=8.4Hz), 3.65(2H,s), 6.30(1H,s), 6.50(1H,d,J=7.2Hz), 6.99-7.04(2H,m), 7.05-7.09(2H,m), 7.16-7.24(2H,m).

342-4) 1-[1-(2-Fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline

Water (10 ml) and conc. sulfuric acid (10 ml) were added to the 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-cyanomethylindoline (6.51 g) obtained above. After dissolution, the resultant mixture was heated under reflux.

Then the reaction solution was ice-cooled and neutralized with an 8 N aqueous solution of sodium hydroxide and the pH value of the mixture was adjusted to pH 6 with 1 N hydrochloric acid. After extracting with chloroform, it was washed with brine and dried over magnesium sulfate. After evaporated the solvent under reduced pressure, the title compound (0.93 g) was obtained as a pale green powder.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 1.91-1.95(2H,m), 2.52(2H,br-s), 2.80(2H,br-s), 2.90(2H,t,J=8.4Hz), 3.13-3.17(2H,m), 3.27-3.31(2H,m), 3.40(2H,t,J=8.4Hz), 3.54-3.73(3H,m), 3.55(2H,s), 6.39(1H,s), 6.55(1H,d,J=7.6Hz), 6.97-7.13(3H,m), 7.25-7.35(2H,m).

ESI-Mass ; 383(MH+).

342-5) 1-[1-(2-Fluorophenethyl)piperidin-4-yl]-6-methylcarbamoylmethylindole

1-[1-(2-Fluorophenethyl)piperidin-4-yl]-6-carboxymethyl-indoline (0.16 g) obtained in Example 146 was dissolved in N,N-dimethylformamide (5 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.08 g) and the resultant mixture was stirred under nitrogen atmosphere at room temperature for 15 min. Next, a 2 N solution (1.02 ml) of methylamine in tetrahydrofuran was added thereto and the resultant mixture was stirred for 2 hr. After evaporating the solvent under reduced pressure, water and ethyl acetate were

added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give pale brown crystals (0.09 g).

The obtained crystals were dissolved in chloroform (20 ml) and manganese dioxide (0.20 g) was added thereto. After stirring the resultant mixture at 50°C overnight, additional manganese dioxide (0.20 g) was added thereto followed by stirring for 7 hr. Next, the manganese dioxide was filtered off and the solvent was evaporated under reduced pressure. The residue was recrystallized from chloroform/n-hexane to give the title compound (0.06 g) as a pale brown powder.

m.p.: 136.5 - 137.4°C.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.08-2.13(4H,m), 2.28-2.35(2H,m), 2.67-2.71(2H,m), 2.73(3H,d,J=4.8Hz), 2.88-2.92(2H,m), 3.20(2H,br-d), 3.72(2H,s), 4.21-4.28(1H,m), 5.40(1H,br-s), 6.53(1H,d,J=3.2Hz), 6.96(1H,dd,J=1.2,8.0Hz), 7.01-7.06(1H,m), 7.06-7.10(1H,m), 7.18-7.24(4H,m), 7.61(1H,d,J=8.0Hz).

ESI-Mass ; 394(MH+).

Example 343: Synthesis of 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-(1-acetylpiperidin-4-yl)methylcarbamoylmethylindole oxalate

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-

carboxymethylindoline (0.20 g) obtained in Example 146 was dissolved in N,N-dimethylformamide (5 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.10 g) and the resultant mixture was stirred under nitrogen atmosphere at room temperature for 15 min. Next, 1-acetyl-4-aminomethyl-piperidine (0.25 g) dissolved in N,N-dimethylformamide (1 ml) was added thereto and the mixture was further stirred overnight. After evaporating the solvent under reduced pressure, water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give a pale brown viscous oil (0.20 g).

The resulting residue was dissolved in chloroform (30 ml) and manganese dioxide (0.33 g) was added thereto. After stirring the resultant mixture at 50°C overnight, additional manganese dioxide (0.17 g) was added thereto followed by stirring for 6 hr. Next, the manganese dioxide was filtered off and the solvent was evaporated under reduced pressure to give the title compound (0.26 g) as a pale yellow amorphous substance.

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 0.94-1.09(2H,m), 1.55-1.83(3H,m), 2.04(3H,s), 2.08-2.13(4H,m), 2.25-2.31(2H,m), 2.46(1H,dt, $J=2.4, 12.8\text{Hz}$), 2.64-2.68(2H,m), 2.81-2.85(2H,m), 2.92-3.03(2H,m), 3.11-3.20(3H,m), 3.72(2H,s), 3.75(1H,br-d),

4.20-4.28(1H,m), 4.55(1H,br-d), 5.55(1H,t,J=6.0Hz),
6.53(1H,d,J=2.8Hz), 6.95-7.01(3H,m), 7.17-7.20(2H,m), 7.26-
7.27(2H,m), 7.62(1H,d,J=8.0Hz).

ESI-Mass ; 519(MH+).

Example 344: Synthesis of 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-ethylcarbamoylmethylindole

1-[1-(2-Fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (0.16 g) obtained in Example 342-4) was dissolved in N,N-dimethylformamide (5 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.08 g) and the resultant mixture was stirred under nitrogen atmosphere at room temperature for 15 min. Next, a 2 N solution (1.06 ml) of ethylamine in tetrahydrofuran was added thereto and the mixture was further stirred for 2 hr. After evaporating the solvent under reduced pressure, water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give pale brown crystals (0.11 g).

These crystals were dissolved in chloroform (20 ml) and manganese dioxide (0.23 g) was added thereto. After stirring the resultant mixture at 50°C overnight, additional manganese dioxide (0.23 g) was added thereto followed by stirring for 7 hr. Next, the manganese dioxide was filtered off and the

solvent was evaporated under reduced pressure. The residue was recrystallized from chloroform/n-hexane to give the title compound (0.07 g) as a pale brown powder.

m.p.: 147.0 - 148.6°C.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 1.02(3H,t,J=7.4Hz), 2.08-2.13(4H,m), 2.28-2.35(2H,m), 2.67-2.71(2H,m), 2.88-2.92(2H,m), 3.19-3.26(4H,m), 3.70(2H,s), 4.21-4.29(1H,m), 5.40(1H,br-t), 6.53(1H,d,J=3.2Hz), 6.97(1H,dd,J=1.6,8.0Hz), 7.01-7.06(1H,m), 7.06-7.10(1H,m), 7.18-7.27(4H,m), 7.61(1H,d,J=8.0Hz).

ESI-Mass ; 408(MH+).

Example 345: Synthesis of 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-(1-ethylpiperidin-4-yl)methylcarbamoylethylindole oxalate

345-1) 1-Acetyl-4-aminomethylpiperidine

Benzene (70 ml) was added to 4-aminomethylpiperidine (10.00 g) followed by dissolution. Next, benzaldehyde (9.30 g) was added thereto and the resultant mixture was heated under reflux for 3 hr with the use of a Dean-Stark reflux condenser. After evaporating the solvent under reduced pressure, benzene (70 ml) was added to the residue followed by dissolution. Next, triethylamine (67 ml) and acetic anhydride (9.1 ml) were added thereto and the resultant mixture was stirred under nitrogen atmosphere at room temperature for 3 days. The solvent was

evaporated under reduced pressure.

Sodium hydrogensulfate monohydrate (13.3 g) was dissolved in water (80 ml) and the resulting residue was added thereto. The resultant mixture was stirred at room temperature for 2.5 hr. Then the reaction solution was washed with ether. The aqueous layer was ice-cooled and the pH value thereof was adjusted to pH 11 with a 5 N aqueous solution of sodium hydroxide followed by extraction with chloroform under salting out. Then the extract was dried over magnesium sulfate and the solvent was evaporated under reduced pressure to give the title compound (12.81 g) as a brown oil.

^1H -NMR (400MHz, CDCl_3) ; δ (ppm) 1.04-1.19 (2H,m) , 1.50-1.57 (1H,m) , 1.74-1.84 (2H,m) , 2.09 (3H,s) , 2.54 (1H,dt,J=2.8,12.8Hz) , 2.62 (2H,d,J=6.8Hz) , 3.04 (1H,dt,J=2.8,12.8Hz) , 3.80-3.86 (1H,m) , 4.61-4.67 (1H,m) .

345-2) 1-Ethyl-4-aminomethylpiperidine

Lithium aluminum hydride (1.06 g) was suspended in tetrahydrofuran (70 ml) and the resultant suspension was stirred under nitrogen atmosphere under ice cooling. Next, 1-acetyl-4-aminomethylpiperidine (4.14 g) dissolved in tetrahydrofuran (30 ml) was added thereto and the resultant mixture was stirred at room temperature for 10 min and heated under reflux overnight. Then the reaction mixtures were ice-cooled and water (1.06 ml) , a 5 N aqueous solution of sodium

hydroxide (1.06 ml) and further water (3.18 ml) were successively added thereto. After stirring, the mixture was diluted with ethyl acetate and the insolubles were filtered off. The residue was purified by NH-silica gel column chromatography (chloroform/methanol system) to give the title compound (3.15 g) as a pale brown oil.

345-3) 1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-(1-ethylpiperidin-4-yl)methylcarbamoylethylmethylindole oxalate

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (0.29 g) obtained in Example 146 was dissolved in N,N-dimethylformamide (5 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.15 g) and the resultant mixture was stirred under nitrogen atmosphere at room temperature for 15 min. Next, 1-ethyl-4-aminomethylpiperidine (0.32 g) dissolved in N,N-dimethylformamide (1 ml) was added thereto and the mixture was stirred for additional 3 hr. After evaporating the solvent under reduced pressure, water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give a pale brown viscous oil (0.30 g).

The obtained residue was dissolved in chloroform (30 ml) and manganese dioxide (0.51 g) was added thereto. After

stirring the resultant mixture at 50°C overnight, additional manganese dioxide (0.51 g) was added thereto followed by stirring for 13.5 hr. After further adding manganese dioxide (0.51 g), the resultant mixture was stirred overnight. Next, the manganese dioxide was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol system) to give a free title compound (0.26 g) as a brown viscous oil, which was then converted into an oxalate in a conventional manner.

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 1.12(3H,t,J=6.6Hz), 1.27-1.35(2H,m), 1.54-1.64(1H,m), 1.73(2H,br-d), 1.92-2.08(4H,m), 2.30(2H,br-t), 2.55(2H,br-t), 2.62-2.66(2H,m), 2.78-2.86(4H,m), 2.97(2H,br-t), 3.14(2H,br-d), 3.23(2H,br-d), 3.50(2H,s), 4.26-4.34(1H,m), 6.40(1H,d,J=3.2Hz), 6.93(1H,d,J=8.0Hz), 7.12(2H,br-t), 7.28-7.32(2H,m), 7.41-7.45(2H,m), 8.09(1H,t,J=5.8Hz).

ESI-Mass ; 505(MH+).

Example 346: Synthesis of 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-(2-hydroxyethyl)carbamoylmethylindole

1-[1-(2-Fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline (0.20 g) obtained in Example 342-4) was dissolved in N,N-dimethylformamide (5 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.10 g) and the

resultant mixture was stirred under nitrogen atmosphere at room temperature for 15 min. Next, ethanolamine (161 ml) was added thereto and the mixture was stirred overnight. After evaporating the solvent under reduced pressure, water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give pale brown crystals (0.14 g).

These crystals were dissolved in chloroform (30 ml) and manganese dioxide (0.28 g) was added thereto. After stirring the resultant mixture at 50°C overnight, the manganese dioxide was filtered off and the solvent was evaporated under reduced pressure. The residue was recrystallized from ethyl acetate/n-hexane to give the title compound (0.07 g) as a pale gray powder.

m.p.: 127.7 - 128.6°C.

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 2.08-2.21(4H,m), 2.31(2H,br-t), 2.68-2.71(2H,m), 2.88-2.92(2H,m), 3.21(2H,br-d), 3.37(2H,dt,J=4.8,4.8Hz), 3.67(2H,t,J=4.8Hz), 3.74(2H,s), 4.20-4.27(1H,m), 5.90(1H,br-s), 6.51(1H,d,J=3.2Hz), 6.96-7.10(3H,m), 7.18-7.26(3H,m), 7.32(1H,s), 7.61(1H,d,J=8.0Hz).
ESI-Mass ; 424(MH+).

Example 347: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1,3-dioxolan-2-yl)methyl carbamoylmethylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-

carboxymethylindoline (0.22 g) obtained in Example 342-4) was dissolved in N,N-dimethylformamide (5 ml). To the resultant solution was added 1,1-carbonyldiimidazole (0.11 g) and the resultant mixture was stirred under nitrogen atmosphere at room temperature for 15 min. Next, 2-aminomethyl-1,3-dioxolane (0.12 g) dissolved in N,N-dimethylformamide (1 ml) was added thereto and the mixture was stirred overnight. After evaporating the solvent under reduced pressure, water and ethyl acetate were added to the residue. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. Then the solvent was evaporated under reduced pressure to give pale brown crystals (0.20 g).

These crystals were dissolved in chloroform (20 ml) and manganese dioxide (0.38 g) was added thereto. After stirring the resultant mixture at 50°C overnight, additional manganese dioxide (0.38 g) was added thereto and the mixture was stirred for 10.5 hr. Next, the manganese dioxide was filtered off and the solvent was evaporated under reduced pressure. The residue was recrystallized from chloroform/n-hexane to give the title compound (0.15 g) as colorless needles.

m.p.: 173.8 - 174.6°C.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.05-2.12(4H,m), 2.25-2.31(2H,m), 2.64-2.68(2H,m), 2.81-2.85(2H,m), 3.18(2H,br-d),

3.43(2H,dd,J=3.6,6.0Hz), 3.73(2H,s), 3.75-3.79(4H,m), 4.21-4.29(1H,m), 4.90(1H,t,J=3.6Hz), 5.67(1H,t,J=6.0Hz), 6.51(1H,d,J=3.2Hz), 6.96-7.01(3H,m), 7.17-7.20(2H,m), 7.25-7.28(2H,m), 7.60(1H,d,J=8.0Hz).

ESI-Mass ; 466(MH+).

Example 348: Synthesis of 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-aminomethylindole

348-1) 1-(2-Fluorophenethyl)piperidin-4-one

An aqueous solution (400 ml) of N,N-dimethyl-4-oxopiperidinium iodide (49.6 g) was added dropwise under reflux into a solution of 2-fluorophenethylamine (25 g) and potassium carbonate (56.6 g) in water (400 ml) and ethanol (800 ml). After the completion of the addition, the reaction solution was further heated under reflux for 45 min. Then ethanol was evaporated under reduced pressure and the residue was extracted with chloroform. The chloroform layer was washed with brine and dried over magnesium sulfate. After evaporating the solvent under reduced pressure, the residue was dissolved in a mixture of ethyl acetate with chloroform (1 : 1) and filtered through silica gel. The filtrate was concentrated under reduced pressure to give the title compound (31.2 g) as a yellow oil (yield: 80.2 %).

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.46-2.55(4H,m), 2.71-2.80(2H,m), 2.80-2.93(6H,m), 6.98-7.10(2H,m), 7.16-

7.25(2H,m).

348-2) 1-[1-(2-Fluorophenethyl)piperidin-4-yl]-6-bromoindoline

*Suly
P231*

Triacetoxylated sodium borohydride (15.0 g) was added under ice cooling to a liquid mixture of 6-bromoindoline (9.0 g), 1-(2-fluorophenethyl)piperidin-4-one (11.0 g) and acetic acid (12.5 ml) in 1,2-dichloroethane (140 ml). Then the reaction mixtures were stirred at room temperature overnight. The reaction mixtures were diluted with ethyl acetate (400 ml) and then an 8 N aqueous solution (70 ml) of sodium hydroxide was added thereto. The organic layer was separated, extracted with 5 N hydrochloric acid (ml) and then basified with an 8 N aqueous solution of sodium hydroxide. Then it was extracted with ethyl acetate and washed successively with water and brine. The ethyl acetate layer was dried over magnesium sulfate and the solvent was evaporated distilled off under reduced pressure to give the title compound (12.2 g) as a pale yellow solid (yield: 66.6 %).

$^1\text{H-NMR}$ (400MHz, DMSO- d_6) ; δ (ppm) 1.52-1.66(4H,m),
2.10(2H,dt,J=7.6,2.8Hz), 2.48-2.53(2H,m), 2.77(2H,t,J=8.4Hz),
2.83(2H,t,J=8.4Hz), 2.96-3.03(2H,br-d), 3.37(2H,t,J=8.4Hz),
3.34-3.43(1H,m), 6.57(1H,d,J=1.2Hz), 6.61(1H,dd,J=7.6,1.2Hz),
6.90(1H,d,J=7.6Hz), 7.10-7.16(2H,m), 7.21-7.28(1H,m),
7.33(1H,dt,J=7.6,1.2Hz).

ESI-Mass ; 404(MH+).

348-3) 1-[1-(2-Fluorophenethyl)piperidin-4-yl]-6-formylindoline

A 1.6 M solution (24 ml) of n-(butyllithium) in hexane was added dropwise at - 78°C over 10 min into a solution of 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-bromoindoline (12 g) obtained in Example 348-2) in tetrahydrofuran (200 ml). After 10 min, dimethylformamide (3.5 ml) was added thereto and the resultant mixture was allowed to warm to room temperature. Then a saturated aqueous solution (100 ml) of ammonium chloride and ethyl acetate (200 ml) were added thereto and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting obtained was purified by silica gel column chromatography (ethyl acetate/ethanol system) to give the title compound (9.6 g) as a yellow powder (yield: 91.5 %).
m.p.: 86 - 87°C.

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 1.56-1.71(4H,m), 2.07-2.16(2H,m), 2.48-2.56(2H,m), 2.77(2H,t,J=8.0Hz), 2.94-3.06(4H,m), 3.39-3.50(3H,m), 6.82(1H,s), 7.10-7.17(3H,m), 7.20-7.29(2H,m), 7.31-7.37(1H,m), 9.83(1H,s).

ESI-Mass ; 353(MH+).

348-4) 1-[1-(2-Fluorophenethyl)piperidin-4-yl]-6-formylindole

10209-6324950
A suspension of 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-formylindoline (2.50 g) obtained in Example 348-3) and activated manganese dioxide (5.0 g) in chloroform (100 ml) was heated under reflux for 4 hr under vigorous stirring. Further, activated manganese dioxide (5.0 g x 1, 2.5 g x 2) was added to the reaction mixture at 1 hr intervals and the resultant mixture was reacted for additional 2 hr. The reaction solution was filtered through celite and the residue was washed with chloroform. The filtrate was concentrated under reduced pressure to give the title compound (1.94 g) as a yellow powder (yield: 78.0 %).

m.p.: 128 - 129°C.

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 2.09-2.42(6H,m), 2.67-2.75(2H,m), 2.83-2.91(2H,m), 3.19-3.28(2H,br-d), 4.35-4.45(1H,m), 6.61(1H,d,J=3.2Hz), 6.95-7.05(2H,m), 7.16-7.23(2H,m), 7.48(1H,d,J=3.2Hz), 7.62(1H,dd,J=8.0,1.2Hz), 7.72(1H,d,J=8.0Hz), 7.98(1H,s), 10.07(1H,s).

Mass ; 351(MH+).

348-5) 1-[1-(2-Fluorophenethyl)piperidin-4-yl]-6-aminomethylindole

A mixture of 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-formylindole (1.94 g) obtained in Example 348-4), hydroxylamine hydrochloride (0.5 g) and anhydrous sodium acetate (0.55 g) in methanol (60 ml) was stirred at room

temperature for 1 hr. Then the reaction mixtures were concentrated and the residue was partitioned between ethyl acetate (150 ml) and a 1 N aqueous solution (30 ml) of sodium hydroxide. The ethyl acetate layer was washed successively with water and brine, dried over magnesium sulfate and concentrated under reduced pressure to give 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-hydroxyiminomethylindole (1.96 g) as an ivory powder (yield: 96.8 %).

A solution of 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-hydroxyiminomethylindole (1.95 g) in tetrahydrofuran (50 ml) was added dropwise at room temperature under ice cooling and stirring into a suspension of lithium aluminum hydride (0.4 g) in tetrahydrofuran (100 ml). Then the resultant mixture was heated under reflux for 3 hr. Under ice water cooling, water (1 ml), a 5 N aqueous solution of sodium hydroxide (3 ml) and further water (1 ml) were carefully added dropwise into the reaction mixtures and the mixture was further vigorously stirred. The resulting precipitate was collected by filtration and washed with tetrahydrofuran. The filtrate was concentrated under reduced pressure. The residue was purified by NH-silica gel column chromatography (ethyl acetate) to give the title compound (0.92 g) as a brown wax (yield: 49.1 %).

$^1\text{H-NMR}$ (400MHz, DMSO- d_6) ; δ (ppm) 1.80-2.04(4H,m), 2.22-2.30(2H,m), 2.56-2.62(2H,m), 2.79-2.85(2H,m), 3.06-

3.13(2H,m), 3.80(2H,s), 4.27-4.38(1H,m), 6.38(1H,d,J=2.8Hz),
6.97(1H,br-d), 7.12-7.18(2H,m), 7.23-7.29(1H,m), 7.34-
7.39(1H,m), 7.41-7.45(2H,m), 7.47(1H,br-s).

Example 349: Synthesis of 1-[1-(4-chlorophenethyl)piperidin-4-yl]-6-acetamidomethylindole

1-[1-(4-Chlorophenethyl)piperidin-4-yl]-6-acetamidomethylindoline (120 mg) obtained in Example 98, activated manganese dioxide (480 mg) and chloroform (10 ml) were treated as in Example 285 to give the title compound (95 mg) as a white powder (yield: 80 %).

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.03(3H,s), 2.04-2.16(4H,m), 2.24-2.40(2H,m), 2.64-2.76(2H,m), 2.81-2.95(2H,m), 3.12-3.29(2H,m), 4.23-4.33(1H,m), 4.55(2H,d,J=5.6Hz), 5.79(1H,br-s), 6.51(1H,d,J=3.6Hz), 7.03(1H,d,J=8.0Hz), 7.17(2H,d,J=8.4Hz), 7.25(1H,d,J=3.6Hz), 7.28(2H,d,J=8.4Hz), 7.36(1H,s), 7.59(1H,d,J=8.0Hz).

m.p.: 148 - 149°C.

Mass: FAB+410(M+H).

Example 350: Synthesis of 1-[1-(3-fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindole

1-[1-(3-Fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindoline (130 mg) obtained in Example 135, activated manganese dioxide (520 mg) and chloroform (10 ml) were treated as in Example 285 to give the title compound (110 mg)

as a white powder (yield: 85 %).

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 2.03(3H,s), 2.04-2.16(4H,m),
2.24-2.40(2H,m), 2.60-2.78(2H,m), 2.80-2.99(2H,m), 3.11-
3.33(2H,m), 4.22-4.33(1H,m), 4.55(2H,d, $J=5.2\text{Hz}$),
5.78(1H,br-s), 6.51(1H,d, $J=3.2\text{Hz}$), 6.89-6.98(2H,m), 7.00-
7.11(2H,m), 7.24-7.30(2H,m), 7.36(1H,s), 7.59(1H,d, $J=8.0\text{Hz}$).

m.p.: 134 - 135°C.

Mass: FAB+394(M+H).

Example 351: Synthesis of 1-[1-(4-methoxyphenethyl)-
piperidin-4-yl]-6-acetamidomethylindole

1-[1-(4-Methoxyphenethyl)piperidin-4-yl]-6-
acetamidomethylindoline (110 mg) obtained in Example 97,
activated manganese dioxide (440 mg) and chloroform (10 ml) were
treated as in Example 285 to give the title compound (90 mg)
as pale yellow prisms (yield: 82 %).

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 2.03(3H,s), 2.05-2.15(4H,m),
2.25-2.35(2H,m), 2.63-2.76(2H,m), 2.79-2.90(2H,m), 3.17-
3.30(2H,m), 3.80(3H,s), 4.22-4.31(1H,m), 4.52(2H,d, $J=5.2\text{Hz}$),
5.73(1H,br-s), 6.51(1H,d, $J=3.6\text{Hz}$), 6.86(2H,d, $J=8.4\text{Hz}$),
7.03(1H,d, $J=8.0\text{Hz}$), 7.16(2H,d, $J=8.4\text{Hz}$), 7.25(1H,d, $J=3.6\text{Hz}$),
7.36(1H,s), 7.59(1H,d, $J=8.0\text{Hz}$).

m.p.: 101 - 102°C.

Mass: FAB+406(M+H).

Example 352: Synthesis of 1-[1-(2-

fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindole

1-[1-(2-Fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindoline (110 mg) obtained in Example 134, activated manganese dioxide (440 mg) and chloroform (10 ml) were treated as in Example 285 to give the title compound (90 mg) as pale yellow needles (yield: 82 %).

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.03(3H,s), 2.05-2.16(4H,m), 2.31-2.43(2H,m), 2.69-2.82(2H,m), 2.86-2.99(2H,m), 3.17-3.31(2H,m), 4.23-4.35(1H,m), 4.55(2H,d,J=5.6Hz), 5.75(1H,br-s), 6.51(1H,d,J=3.6Hz), 6.99-7.13(3H,m), 7.15-7.27(3H,m), 7.37(1H,s), 7.59(1H,d,J=8.0Hz).

m.p.: 101 - 102°C.

Mass: FAB+394(M+H).

Example 353: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2,4-imidazolidinedion-3-yl)methylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-(2,4-imidazolidinedion-3-yl)methylindoline (110 mg) obtained in Example 207, activated manganese dioxide (550 mg) and chloroform (10 ml) were treated as in Example 285 to give the title compound (80 mg) as a pale yellow powder (yield: 74 %).

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.05-2.13(4H,m), 2.26-2.36(2H,m), 2.63-2.70(2H,m), 2.80-2.87(2H,m), 3.14-3.20(2H,m), 3.93(2H,s), 4.21-4.33(1H,m), 4.79(2H,s), 5.83(1H,br-s), 6.49(1H,d,J=3.2Hz), 6.96-7.03(2H,m), 7.15-

7.22(3H,m), 7.25(1H,d,J=3.2Hz), 7.48(1H,s),

7.56(1H,d,J=8.0Hz).

m.p.: 156 - 157°C.

Mass: FAB+435(M+H).

Example 354: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-isobutyrylaminomethylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-isobutyrylaminomethylindoline (110 mg) obtained in Example 158, activated manganese dioxide (550 mg) and chloroform (10 ml) were treated as in Example 285 to give the title compound (95 mg) as white needles (yield: 87 %).

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 1.19(6H,d,J=7.6Hz), 2.06-2.15(4H,m), 2.26-2.43(2H,m), 2.38(1H,septet,J=7.6Hz), 2.65-2.75(2H,m), 2.81-2.91(2H,m), 3.18-3.27(2H,m), 4.22-4.31(1H,m), 4.56(2H,d,J=5.6Hz), 5.75(1H,br-s), 6.51(1H,d,J=3.2Hz), 6.96-7.05(3H,m), 7.16-7.22(2H,m), 7.25(1H,d,J=3.2Hz), 7.33(1H,s), 7.59(1H,d,J=8.0Hz).

m.p.: 97 - 98°C.

Mass: FAB+422(M+H).

Example 355: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-imidazolidonyl)methylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-(2-imidazolidonyl)methylindoline (80 mg) obtained in Example 206, activated manganese dioxide (400 mg) and chloroform (10 ml) were

treated as in Example 285 to give the title compound (32 mg) as a pale yellow powder (yield: 48 %).

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 2.04-2.18(4H,m), 2.28-2.42(2H,m), 2.65-2.78(2H,m), 2.81-2.96(2H,m), 3.12-3.41(6H,m), 4.25-4.36(2H,m), 4.49(2H,s), 6.52(1H,d,J=3.2Hz), 6.99(1H,d,J=8.0Hz), 7.00-7.09(2H,m), 7.17-7.23(2H,m), 7.26(1H,d,J=3.2Hz), 7.33(1H,s), 7.58(1H,d,J=8.0Hz).

m.p.: 130 - 131°C.

Mass: FAB+421(M+H).

Example 356: Synthesis of 1-{1-[4-(4-fluorophenyl)butyl]piperidin-4-yl}-6-acetamidomethylindole

1-{1-[4-(4-Fluorophenyl)butyl]piperidin-4-yl}-6-acetamidomethylindoline (110 mg) obtained in Example 227, activated manganese dioxide (550 mg) and chloroform (10 ml) were treated as in Example 285 to give the title compound (56 mg) as a white powder (yield: 51 %).

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 1.62-1.72(4H,m), 2.04(3H,s), 2.05-2.17(4H,m), 2.24-2.39(2H,m), 2.60-2.79(2H,m), 2.81-2.92(2H,m), 3.10-3.22(2H,m), 4.23-4.35(1H,m), 4.55(2H,d,J=5.6Hz), 5.83(1H,br-s), 6.50(1H,d,J=3.2Hz), 6.95-7.01(2H,m), 7.03(1H,d,J=8.0Hz), 7.12-7.17(2H,m), 7.23(1H,d,J=3.2Hz), 7.26(1H,s), 7.58(1H,d,J=8.0Hz).

m.p.: 59 - 60°C.

Mass: FAB+422(M+H).

Example 357: Synthesis of 1-[1-(2,4-difluorophenethyl)-piperidin-4-yl]-6-acetamidomethylindole

1-[1-(2,4-Difluorophenethyl)piperidin-4-yl]-6-acetamidomethylindoline (100 mg) obtained in Example 224, activated manganese dioxide (500 mg) and chloroform (10 ml) were treated as in Example 285 to give the title compound (83 mg) as an oil. This oil was then crystallized from ethyl acetate by using oxalic acid (15 mg) to give the oxalate (46 mg) of the title compound as pale yellow prisms (yield: 42 %).

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 2.00-2.28(4H,m), 2.05(3H,s), 2.81-3.16(6H,m), 3.44-3.54(2H,m), 4.28(2H,d,J=5.2Hz), 4.52-4.63(1H,m), 6.47(1H,d,J=3.6Hz), 6.99-7.16(3H,m), 7.32-7.40(1H,m), 7.44(1H,d,J=3.6Hz), 7.51-7.58(2H,m), 8.23(1H,t,J=5.2Hz).

m.p.: 103 - 106°C.

Mass: FAB+412(M+H).

Example 358: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-pyrrolidon-1-yl)methylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-(2-pyrrolidon-1-yl)methylindoline (80 mg) obtained in Example 202, activated manganese dioxide (400 mg) and chloroform (10 ml) were treated as in Example 285 to give the title compound (69 mg) as an oil. This oil was then crystallized from ethyl acetate by using oxalic acid (13 mg) to give the oxalate (54 mg) of the

title compound as a white powder (yield: 61 %).

$^1\text{H-NMR}$ (400MHz,DMSO- d_6) ; δ (ppm) 1.83-1.92(2H,m), 2.05-2.25(4H,m), 2.27(2H,t,J=8.0Hz), 2.89-3.24(6H,m), 3.20(2H,t,J=8.0Hz), 3.46-3.56(2H,m), 4.44(2H,s), 4.54-4.66(1H,m), 6.45(1H,d,J=2.8Hz), 6.89(1H,d,J=8.0Hz), 7.13-7.19(2H,m), 7.30-7.36(2H,m), 7.40-7.46(2H,m), 7.50(1H,d,J=8.0Hz).

m.p.: 179 - 180°C.

Mass: FAB+420(M+H).

Example 359: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-N-methylacetamidomethylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-N-methylacetamidomethylindoline (140 mg) obtained in Example 163, activated manganese dioxide (700 mg) and chloroform (10 ml) were treated as in Example 285 to give the title compound (120 mg) as an oil. This oil was then crystallized from ethyl acetate by using oxalic acid (24 mg) to give the oxalate (90 mg) of the title compound as a pale red powder (yield: 58 %).

$^1\text{H-NMR}$ (400MHz,DMSO- d_6) ; δ (ppm) 2.05(1.5H,s), 2.10(1.5H,s), 2.05-2.26(4H,m), 2.78(1.5H,s), 2.87(1.5H,s), 2.90-3.04(4H,m), 3.09-3.18(2H,m), 3.46-3.56(2H,m), 4.52-4.66(3H,m), 6.44(0.5H,d,J=2.8Hz), 6.47(0.5H,d,J=2.8Hz), 6.86-6.92(1H,m), 7.13-7.20(2H,m), 7.30-7.46(4H,m), 7.48(0.5H,d,J=8.0Hz), 7.53(0.5H,d,J=8.0Hz).

m.p.: 148 - 149°C.

Mass: FAB+408(M+H).

Example 360: Synthesis of 1-{1-[3-(4-fluorophenyl)propyl]-piperidin-4-yl}-6-acetamidomethylindole

1-{1-[3-(4-Fluorophenyl)propyl]piperidin-4-yl}-6-acetamidomethylindoline (110 mg) obtained in Example 226, activated manganese dioxide (550 mg) and chloroform (10 ml) were treated as in Example 285 to give the title compound (113 mg) as an oil. This oil was crystallized from diethyl ether with the use of oxalic acid (25 mg) to give the oxalate (90 mg) of the title compound as a pale red amorphous substance (yield: 67 %).

$^1\text{H-NMR}$ (400MHz, DMSO- d_6) ; δ (ppm) 1.84(3H,s), 1.87-1.97(2H,m), 2.01-2.09(2H,m), 2.14-2.26(2H,m), 2.60-2.67(2H,m), 2.86-2.99(4H,m), 3.41-3.50(2H,m), 4.32(2H,d,J=5.6Hz), 4.53-4.61(1H,m), 6.43(1H,d,J=3.2Hz), 6.94(1H,d,J=8.0Hz), 7.08-7.15(2H,m), 7.24-7.30(2H,m), 7.39(1H,d,J=3.2Hz), 7.40(1H,s), 7.47(1H,d,J=8.0Hz), 8.30(1H,t,J=5.6Hz).

Mass ; FAB+ 408(M+H).

Example 361: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-N-methylaminomethylindole

A mixture of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-formylindole (400 mg) obtained in Example 130, methylamine hydrochloride (150 mg), sodium

triacetoxyborohydride (480 mg), acetic acid (300 mg) and dichloroethane (10 ml) was stirred at room temperature for 2 days. Then a saturated aqueous solution of sodium bicarbonate and ethyl acetate were added to the reaction mixtures. The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by Chromatorex NH-silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (140 mg) as an oil. This oil was crystallized from ethyl acetate by using oxalic acid (34 mg) to give the oxalate (140 mg) of the title compound as a white powder (yield: 27 %).

$^1\text{H-NMR}$ (400MHz, DMSO- d_6) ; δ (ppm) 1.88-2.05(4H,m), 2.16-2.25(2H,m), 2.41(3H,s), 2.53-2.60(2H,m), 2.73-2.78(2H,m), 3.04-3.12(2H,m), 3.96(2H,s), 4.20(1H,br-s), 4.24-4.34(1H,m), 6.42(1H,d,J=3.2Hz), 7.02(1H,d,J=8.0Hz), 7.06-7.13(2H,m), 7.25-7.30(2H,m), 7.49(1H,d,J=3.2Hz), 7.50(1H,d,J=8.0Hz), 7.55(1H,s).

m.p.: 195 - 196°C.

Mass: FAB+366(M+H).

Example 362: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(n-butyryl)aminomethylindole

A mixture of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminomethylindole (200 mg) obtained in Example 322-3),

n-butyric anhydride (158 mg) and pyridine (3 ml) was stirred at room temperature for 2 days. Then a saturated aqueous solution of sodium bicarbonate and ethyl acetate were added to the liquid reaction mixture. The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (170 mg) as an oil. This oil was crystallized from ethyl acetate by using oxalic acid (36 mg) to give the oxalate (170 mg) of the title compound as a white amorphous substance (yield: 58 %).

$^1\text{H-NMR}$ (400MHz,DMSO- d_6) ; δ (ppm) 0.85(3H,t,J=7.2Hz), 1.53(2H,q,J=7.2Hz), 1.98-2.18(6H,m), 2.69-3.02(6H,m), 3.35-3.44(2H,m), 4.34(2H,d,J=6.0Hz), 4.41-4.53(1H,m), 6.42(1H,d,J=3.2Hz), 6.93(1H,d,J=8.4Hz), 7.10-7.18(2H,m), 7.27-7.35(2H,m), 7.39(1H,s), 7.42(1H,d,J=3.2Hz), 7.47(1H,d,J=8.4Hz), 8.26(1H,t,J=6.0Hz).

Mass: FAB+422(M+H).

Example 363: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-cyclopropanecarboxamidomethylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-cyclopropanecarboxamidomethylindoline (90 mg) obtained in Example 159, activated manganese dioxide (450 mg) and chloroform (10 ml) were treated as in Example 285 to give the

title compound (60 mg) as a white powder (yield: 73 %).

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 0.72-0.79(2H,m), 0.99-1.04(2H,m), 1.31-1.42(1H,m), 2.05-2.17(4H,m), 2.22-2.35(2H,m), 2.63-2.75(2H,m), 2.82-2.93(2H,m), 3.12-3.25(2H,m), 4.23-4.34(1H,m), 4.58(2H,d, $J=5.6\text{Hz}$), 5.89(1H,br-s), 6.51(1H,d, $J=3.2\text{Hz}$), 6.97-7.03(2H,m), 7.06(1H,d, $J=8.0\text{Hz}$), 7.17-7.23(2H,m), 7.25(1H,d, $J=3.2\text{Hz}$), 7.36(1H,s), 7.60(1H,d, $J=8.0\text{Hz}$).

m.p.: 116 - 117°C.

Mass: FAB+420(M+H).

Example 364: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-hydroxyacetamidomethylindole

A mixture of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminomethylindole (150 mg) obtained in Example 322-3), acetoxyacetyl chloride (64 mg), pyridine (3 ml) and tetrahydrofuran (5 ml) was stirred under ice cooling for 30 min. Then ice water and ethyl acetate were added to the reaction mixtures. The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. To the resulting residue were added methanol (10 ml) and potassium carbonate (100 mg) followed by stirring for 30 min. Then ice water and ethyl acetate were added to the reaction mixtures. The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate and

concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate/ethanol system) to give the title compound (140 mg) as white scales (yield: 80 %).

$^1\text{H-NMR}$ (400MHz, DMSO- d_6) ; δ (ppm) 1.87-1.99(4H,m), 2.19-2.25(2H,m), 2.52-2.59(2H,m), 2.72-2.78(2H,m), 3.03-3.11(2H,m), 3.82(2H,d,J=6.0Hz), 4.23-4.33(1H,m), 4.37(2H,d,J=6.0Hz), 5.48(1H,t,J=6.0Hz), 6.38(1H,d,J=3.2Hz), 6.95(1H,d,J=8.0Hz), 7.06-7.13(2H,m), 7.24-7.30(2H,m), 7.42(1H,d,J=8.0Hz), 7.45(1H,d,J=3.2Hz), 7.46(1H,s), 8.14(1H,t,J=6.0Hz).

m.p.: 76 - 78°C.

Mass: FAB+410(M+H).

Example 365: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-difluoroacetamidomethylindole

Under ice cooling, N,N'-carbonyldiimidazole (160 mg) was added to a solution of difluoroacetic acid (96 mg) in dimethylformamide (5 ml) and the resultant mixture was stirred for 30 min. Next, a solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminomethylindole (150 mg) obtained in Example 322-3) in dimethylformamide (5 ml) was added thereto and the resultant mixture was stirred at room temperature for 2 hr. Then a saturated aqueous solution of sodium bicarbonate and ethyl acetate were added to the reaction

mixtures. The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (120 mg) as a white powder (yield: 65 %).

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 2.05-2.15(4H,m), 2.24-2.35(2H,m), 2.63-2.70(2H,m), 2.79-2.86(2H,m), 3.14-3.22(2H,m), 4.20-4.30(1H,m), 4.62(2H,d, $J=5.6\text{Hz}$), 5.95(1H,t, $J=54.2\text{Hz}$), 6.52(1H,d, $J=3.6\text{Hz}$), 6.61(1H,br-s), 6.96-7.02(2H,m), 7.03(1H,d, $J=8.0\text{Hz}$), 7.15-7.21(2H,m), 7.27(1H,d, $J=3.6\text{Hz}$), 7.33(1H,s), 7.61(1H,d, $J=8.0\text{Hz}$).

m.p.: 79 - 80°C.

Mass: FAB+430(M+H).

Example 366: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-fluoroacetamidomethylindole

Under ice cooling, ethyl chlorocarbonate (96 μl) was added to a suspension of sodium fluoroacetate (100 mg) in dimethylformamide (5 ml) and the resultant mixture was stirred for 20 min. Next, a solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminomethylindole (150 mg) obtained in Example 322-3) in dimethylformamide (5 ml) was added thereto and the resultant mixture was stirred at room temperature for 2 hr. Then a saturated aqueous solution of sodium bicarbonate and ethyl acetate were added to the reaction

mixtures. The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (100 mg) as a white powder (yield: 57 %).

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 2.08-2.16(4H,m), 2.26-2.35(2H,m), 2.64-2.71(2H,m), 2.81-2.88(2H,m), 3.16-3.24(2H,m), 4.21-4.31(1H,m), 4.63(2H,d,J=5.6Hz), 4.85(2H,d,J=47.6Hz), 6.52(1H,d,J=3.2Hz), 6.60(1H,br-s), 6.96-7.02(2H,m), 7.04(1H,d,J=8.0Hz), 7.16-7.21(2H,m), 7.27(1H,d,J=3.2Hz), 7.34(1H,s), 7.61(1H,d,J=8.0Hz).

m.p.: 106 - 108°C.

Mass: FAB+412(M+H).

Example 367: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(3-chloropropionylamino)methylindole

Under ice cooling, a mixture of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminomethylindole (150 mg) obtained in Example 322-3), 3-chloropropionyl chloride (70 mg) and pyridine (5 ml) was stirred for 2 hr. Then a saturated aqueous solution of sodium bicarbonate and ethyl acetate were added to the reaction mixtures. The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl

acetate/methanol system) to give the title compound (30 mg) as a white powder (yield: 16 %).

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 2.04-2.15(4H,m), 2.22-2.32(2H,m), 2.62-2.69(2H,m), 2.65(2H,t, $J=6.4\text{Hz}$), 2.80-2.87(2H,m), 3.13-3.22(2H,m), 3.86(2H,t, $J=6.4\text{Hz}$), 4.20-4.30(1H,m), 4.59(2H,d, $J=5.6\text{Hz}$), 5.99(1H,br-s), 6.51(1H,d, $J=3.2\text{Hz}$), 6.97(1H,d, $J=8.0\text{Hz}$), 6.98-7.04(2H,m), 7.16-7.21(2H,m), 7.24(1H,d, $J=3.2\text{Hz}$), 7.35(1H,s), 7.58(1H,d, $J=8.0\text{Hz}$).

m.p.: 121 - 122°C.

Mass: FAB+442(M+H).

Example 368: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-imidazocarbonylaminomethylindole

Under ice cooling, N,N'-carbonyldiimidazole (160 mg) was added to a solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminomethylindole (150 mg) obtained in Example 322-3) in dimethylformamide (5 ml) and the resultant mixture was stirred for 30 min. Then ice water and ethyl acetate were added to the reaction mixtures. The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate/ethanol system) to give the title compound (140 mg) as an oil. This oil was then crystallized

from ethyl acetate by using oxalic acid (28 mg) to give the oxalate (150 mg) of the title compound as a white powder (yield: 65 %).

$^1\text{H-NMR}$ (400MHz, DMSO- d_6) ; δ (ppm) 1.99-2.23(4H,m), 2.69-2.81(2H,m), 2.84-3.02(4H,m), 3.33-3.43(2H,m), 4.47-4.57(1H,m), 4.54(2H,d,J=5.6Hz), 6.44(1H,d,J=2.8Hz), 7.01(1H,s), 7.03(1H,d,J=8.0Hz), 7.10-7.18(2H,m), 7.27-7.35(2H,m), 7.45(1H,d,J=2.8Hz), 7.51(1H,d,J=8.0Hz), 7.53(1H,s), 7.71(1H,s), 8.27(1H,s), 9.08(1H,t,J=5.6Hz).

m.p.: 156 - 157°C.

Mass: FAB+446(M+H).

Example 369: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(3-hydroxypropionylamino)methylindole

A mixture of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminomethylindole (150 mg) obtained in Example 322-3), β -propiolactone (30 mg) and toluene (10 ml) was heated under reflux for 2 hr. Then the reaction solution was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate/ethanol system) to give the title compound (150 mg) as an oil. This oil was then crystallized from ethyl acetate by using oxalic acid (32 mg) to give the oxalate (100 mg) of the title compound as a pale yellow amorphous substance (yield: 45 %).

$^1\text{H-NMR}$ (400MHz, DMSO- d_6) ; δ (ppm) 2.03-2.25(4H,m),

2.29(2H,t,J=6.8Hz), 2.91-2.98(4H,m), 3.05-3.16(2H,m), 3.44-3.54(2H,m), 3.64(2H,t,J=6.8Hz), 4.35(2H,d,J=6.0Hz), 4.50-4.60(1H,m), 6.43(1H,d,J=3.2Hz), 6.94(1H,d,J=8.4Hz), 7.12-7.20(2H,m), 7.29-7.36(2H,m), 7.41(1H,d,J=3.2Hz), 7.43(1H,s), 7.46(1H,d,J=8.4Hz), 8.28(1H,t,J=6.0Hz).

Mass ; FAB+ 424(M+H).

Example 370: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-3-formyl-6-acetamidomethylindole

Phosphorus oxychloride (0.1 g) was added at 0°C to a solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindole (0.22 g) obtained in Example 285 in N,N-dimethylformamide (5 ml). The resultant mixture was stirred for 10 min and then reacted at 70°C for 2 hr. After adding a 2 N aqueous solution of sodium hydroxide (20 ml), the reaction solution was extracted with ethyl acetate. The extract was washed successively with water and brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue was filtered through silica gel (15 g) and washed with ethyl acetate/methanol. The filtrate was concentrated to give the title compound (0.16 g) as a pale yellow amorphous substance (yield: 67.9 %).

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 2.04(3H,s), 2.14-2.37(4H,m), 2.37-2.49(2H,m), 2.73-2.82(2H,m), 2.87-2.95(2H,m), 3.25-3.35(2H,m), 4.28-4.38(1H,m), 4.55(2H,d,J=5.6Hz), 6.00-

2.29(2H,t,J=6.8Hz), 2.91-2.98(4H,m), 3.05-3.16(2H,m), 3.44-3.54(2H,m), 3.64(2H,t,J=6.8Hz), 4.35(2H,d,J=6.0Hz), 4.50-4.60(1H,m), 6.43(1H,d,J=3.2Hz), 6.94(1H,d,J=8.4Hz), 7.12-7.20(2H,m), 7.29-7.36(2H,m), 7.41(1H,d,J=3.2Hz), 7.43(1H,s), 7.46(1H,d,J=8.4Hz), 8.28(1H,t,J=6.0Hz).

Mass ; FAB+ 424(M+H).

Example 370: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-3-formyl-6-acetamidomethylindole

Phosphorus oxychloride (0.1 g) was added at 0°C to a solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindole (0.22 g) obtained in Example 285 in N,N-dimethylformamide (5 ml). The resultant mixture was stirred for 10 min and then reacted at 70°C for 2 hr. After adding a 2 N aqueous solution of sodium hydroxide (20 ml), the reaction solution was extracted with ethyl acetate. The extract was washed successively with water and brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue was filtered through silica gel (15 g) and washed with ethyl acetate/methanol. The filtrate was concentrated to give the title compound (0.16 g) as a pale yellow amorphous substance (yield: 67.9 %).

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 2.04(3H,s), 2.14-2.37(4H,m), 2.37-2.49(2H,m), 2.73-2.82(2H,m), 2.87-2.95(2H,m), 3.25-3.35(2H,m), 4.28-4.38(1H,m), 4.55(2H,d,J=5.6Hz), 6.00-

6.12(1H,m), 6.97-7.04(2H,m), 7.17-7.24(3H,m), 7.44(1H,br-s),
7.84(1H,s), 8.25(1H,d,J=8.0Hz), 9.97(1H,s).

ESI-Mass ; 422(MH+).

Example 371: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-3-hydroxyimino-6-acetamidomethylindole

A liquid mixture of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-3-formyl-6-acetamidomethylindole (0.09 g) obtained in Example 370, hydroxylamine hydrochloride (0.02 g) and anhydrous sodium acetate (0.03 g) in methanol (10 ml) was stirred at room temperature for 1 hr. Then the reaction mixtures were concentrated and the residue was partitioned between ethyl acetate (20 ml) and a 1 N aqueous solution (10 ml) of sodium hydroxide. The ethyl acetate layer was washed successively with water and brine, dried over magnesium sulfate and concentrated under reduced pressure. Then the residue was crystallized from ether/hexane, collected by filtration, washed with hexane and dried to give the title compound (0.08 g) as a pale yellow powder (yield: 88.5 %).

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 1.87(3H,s), 1.91-2.03(4H,m), 2.20-2.30(2H,m), 2.56-2.62(2H,m), 2.74-2.80(2H,m), 3.06-3.3(2H,m), 4.33-4.38(1H,m), 7.03-7.15(3H,m), 7.27-7.33(2H,m), 7.45-7.50(1H,m), 7.77(1H,d,J=8.0Hz), 7.83(0.5H,d,J=8.0Hz), 7.91(0.5H,d,J=8.0Hz), 8.20(0.5H,s), 8.26(0.5H,s), 8.30-

8.35(1H,m), 10.54(0.5H,s), 11.27(0.5H,s).

Example 372: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-3-hydroxymethyl-6-acetamidomethylindole

Sodium borohydride (0.01 g) was added to a solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-3-formyl-6-acetamidomethylindole (0.04 g) obtained in Example 370 in methanol (10 ml) and the resultant mixture was stirred at room temperature for 0.5 hr. Then the reaction solution was concentrated and the residue was partitioned between ethyl acetate (40 ml) and water (10 ml). The ethyl acetate layer was washed successively with water and brine, dried over magnesium sulfate and concentrated under reduced pressure. Then the residue was treated with ether/hexane to give the title compound (0.03 g) as a pale yellow amorphous substance (yield: 74.6 %). $^1\text{H-NMR}$ (400MHz,DMSO- d_6) ; δ (ppm) 1.86(3H,s), 1.87-2.00(4H,m), 2.18-2.27(2H,m), 2.54-2.61(2H,m), 3.05-3.12(2H,m), 4.22-4.32(1H,m), 4.33(2H,d,J=5.6Hz), 4.60(2H,d,J=5.6Hz), 4.76(1H,t,J=5.6Hz), 6.94(1H,dd,J=8.0,1.2Hz), 7.08-7.15(2H,m), 7.25-7.33(2H,m), 7.36(1H,br-d), 8.26-8.32(1H,m).

Example 373: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-chloroacetamidomethylindole

A mixture of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminomethylindole (150 mg) obtained in Example 322-3), chloroacetyl chloride (60 mg), triethylamine (50 mg) and

acetonitrile (5 ml) was stirred under ice cooling for 2 hr. Then a saturated aqueous solution of sodium bicarbonate and ethyl acetate were added to the reaction solution. The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (90 mg) as white needles (yield: 49 %).

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 2.06-2.13(4H,m), 2.24-2.33(2H,m), 2.63-2.69(2H,m), 2.80-2.86(2H,m), 3.14-3.22(2H,m), 4.09(2H,s), 4.20-4.30(1H,m), 4.59(2H,d, $J=5.6\text{Hz}$), 6.52(1H,d, $J=3.2\text{Hz}$), 6.89(1H,br-s), 6.90-7.02(2H,m), 7.04(1H,d, $J=8.0\text{Hz}$), 7.16-7.21(2H,m), 7.26(1H,d, $J=3.2\text{Hz}$), 7.33(1H,s), 7.61(1H,d, $J=8.0\text{Hz}$).

m.p.: 143 - 144°C.

Mass: FAB+428(M+H).

Example 374: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-bromoacetamidomethylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-aminomethylindole (370 mg) obtained in Example 322-3), bromoacetyl chloride (220 mg), triethylamine (140 mg) and acetonitrile (10 ml) were treated as in Example 373 to give the title compound (320 mg) as an oil (yield: 65 %).

$^1\text{H-NMR}$ (400MHz, CDCl_3) ; δ (ppm) 2.05-2.13(4H,m), 2.25-

2.33(2H,m), 2.62-2.70(2H,m), 2.79-2.85(2H,m), 3.15-
3.24(2H,m), 3.92(2H,s), 4.19-4.29(1H,m), 4.58(2H,d,J=5.6Hz),
6.53(1H,d,J=3.2Hz), 6.90(1H,br-s), 6.92-7.04(3H,m), 7.15-
7.21(2H,m), 7.25(1H,d,J=3.2Hz), 7.34(1H,s),
7.60(1H,d,J=8.0Hz).

Example 375: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(N,N-dimethylaminoacetamido)methylindole

A mixture of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-bromoacetamidomethylindole (170 mg) obtained in Example 374, a 2 M solution (2.2 ml) of dimethylamine in tetrahydrofuran and dimethylformamide (5 ml) was stirred at room temperature for 2 hr. Then water and ethyl acetate were added to the reaction solution. The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by Chromatorex NH silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (35 mg) as an oil.

This oil was crystallized from ethyl acetate by using oxalic acid (7 mg) to give the oxalate (18 mg) of the title compound as a white powder (yield: 9.4 %).

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 1.96-2.16(4H,m), 2.39-
2.44(2H,m), 2.60(6H,s), 2.82-2.94(4H,m), 3.30-3.71(4H,m),
4.41(2H,d,J=5.6Hz), 4.42-4.52(1H,m), 6.43(1H,d,J=2.8Hz),

6.96(1H,d,J=8.0Hz), 7.10-7.19(2H,m), 7.27-7.34(2H,m),
7.45(1H,s), 7.46(1H,d,J=2.8Hz), 7.49(1H,d,J=8.0Hz),
8.53(1H,t,J=5.6Hz).

m.p.: 112 - 113°C.

Mass: FAB+437(M+H).

Example 376: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[(piperidin-1-yl)acetamidomethyl]indole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-bromoacetamidomethylindole (150 mg) obtained in Example 374, piperidine (187 mg) and dimethylformamide (5 ml) were treated as in Example 375 to give the oxalate (20 mg) of the title compound as a white powder (yield: 11 %).

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 1.40-1.50(2H,m), 1.60-1.71(4H,m), 2.00-2.08(2H,m), 2.12-2.26(2H,m), 2.37-2.52(2H,m), 2.70-3.10(8H,m), 3.39-3.49(2H,m), 3.52-3.63(2H,m), 4.42(2H,d,J=6.0Hz), 4.45-4.58(1H,m), 6.43(1H,d,J=3.2Hz), 6.96(1H,d,J=8.0Hz), 7.10-7.19(2H,m), 7.26-7.34(2H,m), 7.44(1H,d,J=3.2Hz), 7.47(1H,s), 7.49(1H,d,J=8.0Hz), 8.76(1H,t,J=6.0Hz).

m.p.: 113 - 114°C.

Mass: FAB+477(M+H).

Example 377: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(3-bromopropionylamino)methylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-

aminomethylindole (370 mg) obtained in Example 322-3), 3-bromopropionyl chloride (240 mg), triethylamine (140 mg) and acetonitrile (10 ml) were treated as in Example 373 to give the title compound (290 mg) as an oil (yield: 57 %).

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.02-2.10(2H,m), 2.14-2.26(2H,m), 2.29-2.40(2H,m), 2.68-2.76(2H,m), 2.80(2H,t,J=6.4Hz), 2.85-2.92(2H,m), 3.18-3.26(2H,m), 3.70(2H,t,J=6.4Hz), 4.20-4.30(1H,m), 4.62(2H,d,J=6.0Hz), 6.15(1H,br-s), 6.50(1H,d,J=3.2Hz), 6.96-7.04(3H,m), 7.16-7.24(2H,m), 7.25(1H,d,J=3.2Hz), 7.37(1H,s), 7.58(1H,d,J=8.0Hz).

Example 378: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(3-N,N-dimethylaminopropionyl)aminomethylindole

A mixture of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(3-bromopropionylamino)methylindole (150 mg) obtained in Example 377, a 2 M solution (5.0 ml) of dimethylamine in tetrahydrofuran and toluene (5 ml) was heated at 80 to 90°C for 1.5 days. Then water and ethyl acetate were added to the reaction mixtures. The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by Chromatorex NH-silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (140 mg) as an oil. This oil was crystallized from ethyl acetate

by using oxalic acid (28 mg) to give the oxalate (110 mg) of the title compound as a white powder (yield: 66 %).

$^1\text{H-NMR}$ (400MHz,DMSO- d_6) ; δ (ppm) 1.90-1.99(2H,m), 2.00-2.12(2H,m), 2.38-2.45(2H,m), 2.55(2H,t,J=7.2Hz), 2.61(6H,s), 2.70-2.76(2H,m), 2.78-2.85(2H,m), 3.11(2H,t,J=7.2Hz), 3.16-3.24(2H,m), 4.37(2H,d,J=5.6Hz), 4.38-4.42(1H,m), 6.40(1H,d,J=2.8Hz), 6.94(1H,d,J=8.0Hz), 7.08-7.14(2H,m), 7.25-7.32(2H,m), 7.42(1H,s), 7.45(1H,d,J=2.8Hz), 7.47(1H,d,J=8.0Hz), 8.58(1H,t,J=5.6Hz).

m.p.: 104 - 105°C.

Mass: FAB+451(M+H).

Example 379: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[3-(piperidin-1-yl)propionylamino]methylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-(3-bromopropionylamino)methylindole (140 mg) obtained in Example 377, piperidine (85 mg) and toluene (5 ml) were treated as in Example 378 to give the oxalate (80 mg) of the title compound as a white powder (yield: 44 %).

$^1\text{H-NMR}$ (400MHz,DMSO- d_6) ; δ (ppm) 1.39-1.49(2H,m), 1.57-1.66(4H,m), 1.90-2.11(4H,m), 2.35-2.60(4H,m), 2.71-3.01(8H,m), 3.06-3.14(2H,m), 3.18-3.25(2H,m), 4.36(2H,d,J=4.8Hz), 4.37-4.45(1H,m), 6.41(1H,d,J=3.2Hz), 6.94(1H,d,J=8.0Hz), 7.06-7.14(2H,m), 7.23-7.31(2H,m), 7.42(1H,s), 7.45(1H,d,J=3.2Hz), 7.47(1H,d,J=8.0Hz),

8.56(1H,t,J=4.8Hz).

m.p.: 108 - 109°C.

Mass: FAB+491(M+H).

Example 380: Synthesis of 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-propionylaminomethylindole

1-[1-(2-Fluorophenethyl)piperidin-4-yl]-6-aminomethylindole (150 mg) obtained in Example 348, propionyl chloride (43 mg), triethylamine (47 mg) and acetonitrile (5 ml) were treated as in Example 373 to give the title compound (105 mg) as a white powder (yield: 60 %).

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 1.19(3H,t,J=7.6Hz), 2.00-2.16(4H,m), 2.25(2H,q,J=7.6Hz), 2.26-2.50(2H,m), 2.61-2.82(2H,m), 2.85-3.05(2H,m), 3.20-3.34(2H,m), 4.19-4.33(1H,m), 4.56(2H,d,J=5.6Hz), 5.75(1H,br-s), 6.51(1H,d,J=3.2Hz), 7.06-7.13(3H,m), 7.15-7.29(3H,m), 7.36(1H,s), 7.59(1H,d,J=8.4Hz).

m.p.: 118 - 119°C.

Mass: FAB+408(M+H).

Example 381: Synthesis of 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-fluoroacetamidomethylindole

1-[1-(2-Fluorophenethyl)piperidin-4-yl]-6-aminomethylindole (150 mg) obtained in Example 348, sodium fluoroacetate (100 mg), ethyl chlorocarbonate (96 μl) and dimethylformamide (10 ml) were treated as in Example 373 to give

the oxalate (100 mg) of the title compound as a white powder (yield: 46 %).

^1H -NMR(400MHz,DMSO- d_6) ; δ (ppm) 2.05-2.12(2H,m), 2.15-2.28(2H,m), 2.93-3.05(4H,m), 3.09-3.17(2H,m), 3.49-3.58(2H,m), 4.41(2H,d,J=6.0Hz), 4.52-4.63(1H,m), 4.83(2H,d,J=47.2Hz), 6.44(1H,d,J=3.2Hz), 6.98(1H,d,J=8.4Hz), 7.15-7.22(2H,m), 7.27-7.35(1H,m), 7.36-7.46(3H,m), 7.48(1H,d,J=8.4Hz), 8.68(1H,t,J=6.0Hz).

m.p.: 168 - 169°C.

Mass: FAB+412(M+H).

Example 382: Synthesis of 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-(3-hydroxypropionylamino)methylindole

1-[1-(2-Fluorophenethyl)piperidin-4-yl]-6-aminomethylindole (110 mg) obtained in Example 348, β -propiolactone (23 mg) and toluene (10 ml) were treated as in Example 373 to give the title compound (90 mg) as a white powder (yield: 69 %).

^1H -NMR(400MHz,CDCl $_3$) ; δ (ppm) 1.99-2.06(4H,m), 2.28-2.39(2H,m), 2.51(2H,t,J=5.2Hz), 2.69-2.78(2H,m), 2.91-2.99(2H,m), 3.23-3.30(2H,m), 3.95(2H,t,J=5.2Hz), 4.14-4.24(1H,m), 4.63(2H,d,J=6.0Hz), 6.28(1H,br-s), 6.45(1H,d,J=3.2Hz), 6.98(1H,d,J=8.8Hz), 7.02-7.12(2H,m), 7.14(1H,d,J=3.2Hz), 7.19-7.27(2H,m), 7.57(1H,d,J=8.8Hz), 7.58(1H,s).

m.p.: 58 - 59°C.

Mass: FAB+424(M+H).

Example 383: Synthesis of 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-hydroxyacetamidomethylindole

1-[1-(2-Fluorophenethyl)piperidin-4-yl]-6-aminomethylindole (150 mg) obtained in Example 348 and acetoxyacetyl chloride (64 mg) were treated as in Example 373 to give the title compound (110 mg) as a white powder (yield: 62 %).

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 1.87-2.03(4H,m), 2.19-2.26(2H,m), 2.54-2.60(2H,m), 2.76-2.83(2H,m), 3.04-3.11(2H,m), 3.82(2H,d,J=6.0Hz), 4.23-4.33(1H,m), 4.37(2H,d,J=6.0Hz), 5.47(1H,t,J=6.0Hz), 6.38(1H,d,J=3.2Hz), 6.95(1H,d,J=8.0Hz), 7.10-7.17(2H,m), 7.21-7.28(1H,m), 7.32-7.38(1H,m), 7.42(1H,d,J=8.0Hz), 7.44(1H,d,J=3.2Hz), 7.45(1H,s), 8.14(1H,t,J=6.0Hz).

m.p.: 151 - 152°C.

Mass: FAB+410(M+H).

Example 384: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methoxycarbonylaminomethylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-aminomethylindole (150 mg) obtained in Example 322-3), methyl chlorocarbonate (47 mg), triethylamine (50 mg) and acetonitrile (5 ml) were treated as in Example 373 to give the title compound

(120 mg) as white needles (yield: 68 %).

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.02-2.12(4H,m), 2.20-2.31(2H,m), 2.60-2.68(2H,m), 2.78-2.85(2H,m), 3.12-3.20(2H,m), 3.70(3H,s), 4.19-4.29(1H,m), 4.48(2H,d,J=6.0Hz), 5.13(1H,br-s), 6.49(1H,d,J=3.2Hz), 6.95-7.01(2H,m), 7.03(1H,d,J=8.0Hz), 7.15-7.20(2H,m), 7.22(1H,d,J=3.2Hz), 7.31(1H,s), 7.58(1H,d,J=8.0Hz).

m.p.: 117 - 118°C.

Mass: FAB+410(M+H).

Example 385: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-N,N-dimethylaminocarbonylaminomethylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-aminomethylindole (150 mg) obtained in Example 322-3), dimethylcarbonyl chloride (54 mg), triethylamine (50 mg) and acetonitrile (5 ml) were treated as in Example 373 to give the title compound (130 mg) as a white powder (yield: 72 %).

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.04-2.11(4H,m), 2.23-2.30(2H,m), 2.62-2.68(2H,m), 2.79-2.85(2H,m), 2.90(6H,s), 3.13-3.20(2H,m), 4.20-4.30(1H,m), 4.53(2H,d,J=5.2Hz), 4.70(1H,br-s), 6.49(1H,d,J=3.2Hz), 6.95-7.02(2H,m), 7.07(1H,d,J=8.0Hz), 7.16-7.21(2H,m), 7.23(1H,d,J=3.2Hz), 7.35(1H,s), 7.58(1H,d,J=8.0Hz).

m.p.: 115 - 116°C.

Mass: FAB+423(M+H).

Example 386: Synthesis of 1-{1-[2-(3-pyridyl)ethyl]-piperidin-4-yl}-6-acetamidomethylindole

386-1) Synthesis of 1-(piperidin-4-yl)-6-acetamidomethylindole

1-(Piperidin-4-yl)-6-acetamidomethylindole (0.6 g) obtained in Production Example 52 and activated manganese dioxide (3.0 g) were heated under reflux in chloroform (30 ml) for 8 hr. Then the reaction mixtures were filtered through celite. The residue was washed with chloroform and the filtrate was concentrated under reduced pressure. The resulting residue was purified by NH-silica gel column chromatography (ethyl acetate/methanol system) to give the title compound (0.45 g) as a brown amorphous substance (yield: 75.5 %).

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 1.75-1.90(4H,m), 1.86(3H,s), 2.64-2.74(2H,m), 3.04-3.10(2H,m), 4.30-4.39(1H,m), 4.33(2H,d,J=6.0Hz), 6.41(1H,d,J=3.0Hz), 6.93(1H,dd,J=8.0,1.2Hz), 7.41(1H,br-s), 7.42(1H,d,J=3.0Hz), 7.47(1H,d,J=8.0Hz), 8.24-8.31(1H,m).

386-2) 1-{1-[2-(3-Pyridyl)ethyl]piperidin-4-yl}-6-acetamidomethylindole

Potassium carbonate (0.5 g) was added to a solution of 1-(piperidin-4-yl)-6-acetamidomethylindole (0.10 g) obtained in Example 386-1) and 3-(2-bromoethyl)pyridine (0.07 g) obtained in Production Example 26-2 in N,N-dimethylformamide

(5 ml) and the resultant mixture was stirred at 70°C for 6 hr. Then the reaction mixtures were concentrated under reduced pressure and the residue was partitioned between ethyl acetate (40 ml) and water (15 ml) followed by extraction with ethyl acetate. The ethyl acetate layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol system) to give the title compound (0.06 g) as a pale yellow wax (yield: 75.5 %).

Then the obtained product was converted into an oxalate in a conventional manner to give the oxalate (0.06 g) of the title compound as a pale yellow amorphous substance.

Oxalate:

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 1.87(3H,s), 2.00-2.09(2H,m), 2.14-2.27(2H,m), 2.75-2.86(2H,m), 2.93-3.09(4H,m), 3.38-3.46(2H,m), 4.35(2H,d,J=6.0Hz), 4.47-4.60(1H,m), 6.44(1H,d,J=3.2Hz), 6.96(1H,d,J=8.0Hz), 7.36(1H,dd,J=8.0,4.4Hz), 7.43-7.47(2H,m), 7.49(1H,d,J=8.0Hz), 7.71-7.76(1H,m), 8.30-8.37(1H,m), 8.46(1H,dd,J=8.0,1.6Hz), 8.53(1H,d,J=1.6Hz).

ESI-Mass ; 377(MH+).

Example 387: Synthesis of 3-cyano-1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-acetamidomethylindole

1,1'-Carbonyldiimidazole (0.04 g) was added to a

1000-6594250
solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-3-hydroxyimino-6-acetamidomethylindole (0.07 g) obtained in Example 371 in chloroform (10 ml) and the resultant mixture was stirred at room temperature for 0.5 hr. Then the reaction mixtures were concentrated and the residue was partitioned between ethyl acetate (40 ml) and water (10 ml). The ethyl acetate layer was washed successively with water and brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by NH-silica gel column chromatography (ethyl acetate) to give the title compound (0.04 g) as a white powder (yield: 57.6 %).

m.p.: 130 - 131°C.

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 1.88(3H,s), 2.09-2.29(4H,m), 2.82-3.14(6H,m), 3.42-3.52(2H,m), 4.39(2H,d,J=5.2Hz), 4.64-4.74(1H,m), 7.14-7.24(3H,m), 7.32-7.38(2H,m), 7.62(1H,d,J=8.4Hz), 7.68(1H,s), 8.43(1H,s).

Example 388: Synthesis of 1-{4-[(1-hydroxyethyl)phenethyl]-piperidin-4-yl}-6-acetamidomethylindole

Potassium carbonate (0.5 g) was added to a solution of 1-(piperidin-4-yl)-6-acetamidomethylindole (0.10 g) obtained in Example 386-1) and 4-(1-hydroxyethyl)phenethyl bromide (0.07 g) obtained in Production Example 19 in N,N-dimethylformamide (5 ml) and the resultant mixture was stirred at 70°C for 6 hr. Then the reaction mixtures were concentrated

under reduced pressure and the residue was partitioned between chloroform (40 ml) and water (15 ml). The chloroform layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol system) to give the title compound (0.07 g) as a pale yellow wax (yield: 45.3 %).

Then the resulting product was converted into an oxalate in a conventional manner to give the oxalate (0.06 g) of the title compound as a pale yellow powder.

Oxalate:

m.p.: 105 - 107°C.

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 1.31(2H,d,J=6.4Hz), 1.87(3H,s), 2.09-2.17(2H,m), 2.30-2.43(2H,m), 2.99-3.05(2H,m), 3.16-3.33(4H,m), 3.62-3.70(2H,m), 4.35(2H,d,J=6.0Hz), 4.64-4.74(2H,m), 6.47(1H,d,J=3.2Hz), 6.97(1H,d,J=8.0Hz), 7.25(2H,d,J=8.0Hz), 7.32(2H,d,J=8.0Hz), 7.43(1H,d,J=3.2Hz), 7.48(1H,br-s), 7.50(1H,d,J=8.0Hz), 8.33-8.38(1H,m).

ESI-Mass ; 420(MH+).

Example 389: Synthesis of 1-[1-(4-bromophenethyl)piperidin-4-yl]-6-acetamidomethylindole

Potassium carbonate (1.0 g) was added to a solution of 1-(piperidin-4-yl)-6-acetamidomethylindole (0.20 g) obtained

in Example 386-1) and 4-bromophenethyl bromide (0.16 g) obtained in Production Example 4 in N,N-dimethylformamide (15 ml) and the resultant mixture was stirred at 70 °C for 6 hr. Then the reaction mixture was concentrated under reduced pressure and the residue was partitioned between chloroform (40 ml) and water (15 ml). The chloroform layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol system) and then crystallized from ethyl acetate/hexane to give the title compound (0.25 g) as a pale yellow powder (yield: 74.6 %). m.p.: 140 - 141°C.

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 1.86(3H,s), 1.88-2.03(4H,m), 2.19-2.28(2H,m), 2.56-2.62(2H,m), 2.73-2.79(2H,m), 3.05-3.12(2H,m), 4.26-4.35(1H,m), 4.34(2H,d,J=6.0Hz), 6.41(1H,d,J=3.2Hz), 6.97(1H,d,J=8.0Hz), 7.25(2H,d,J=8.0Hz), 7.32(2H,d,J=8.0Hz), 4.64-6.93(1H,dd,J=8.0,1.2Hz), 7.23(2H,d,J=8.0Hz), 7.40(1H,br-s), 7.45-7.50(4H,m), 8.25-8.31(1H,m).

ESI-Mass ; 455 (MH+).

Example 390: Synthesis of 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-formylindole

1-[1-(2-Fluorophenethyl)piperidin-4-yl]-6-hydroxymethylindole (0.49 g) obtained in Example 342-1) was

dissolved in chloroform (40 ml). To the resultant solution was added manganese dioxide (1.20 g) and the resultant mixture was stirred at 50°C overnight. After adding additional manganese dioxide (0.60 g), the mixture was further stirred for 7 hr. After further adding manganese dioxide (0.60 g), the mixture was stirred overnight. After furthermore adding manganese dioxide (0.60 g), the mixture was stirred for 10 hr. After furthermore adding manganese dioxide (0.60 g), the mixture was stirred overnight. Next, the manganese dioxide was filtered off and the solvent was evaporated under reduced pressure to give the title compound (0.40 g) as a pale yellow powder.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.07-2.13(4H,m), 2.27-2.34(2H,m), 2.67-2.71(2H,m), 2.87-2.91(2H,m), 3.19(2H,br-d), 4.32-4.40(1H,m), 6.59(1H,d,J=3.2Hz), 7.00-7.03(1H,m), 7.05-7.10(1H,m), 7.17-7.25(2H,m), 7.46(1H,d,J=3.2Hz), 7.61(1H,dd,J=0.8,8.0Hz), 6.71(1H,d,J=8.0Hz), 7.97(1H,s), 10.06(1H,s).

ESI-Mass ; 351(MH+).

Example 391: Synthesis of 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-hydroxymethylindole

1-[1-(2-Fluorophenethyl)piperidin-4-yl]-6-formylindole (0.21 g) obtained in Example 348-4) was dissolved in methanol (10 ml) and tetrahydrofuran (5 ml) and the resultant solution was stirred under ice cooling. Then sodium

borohydride was added thereto in portions. After confirming the disappearance of the starting material by thin layer chromatography, the solvent was evaporated under reduced pressure. Then a 2 N aqueous solution of sodium hydroxide was added to the residue followed by extraction with ethyl acetate. The extract was washed successively with water and brine and dried over magnesium sulfate. After evaporating the solvent under reduced pressure, the residue was recrystallized from chloroform/n-hexane to give the title compound (0.17 g) as a colorless powder.

m.p.: 116.8 - 117.5°C.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.07-2.16(4H,m), 2.26-2.33(2H,m), 2.66-2.70(2H,m), 2.87-2.91(2H,m), 3.19(2H,br-d), 4.23-4.31(1H,m), 4.82(2H,s), 6.51(1H,d,J=3.6Hz), 7.01-7.11(3H,m), 7.17-7.26(3H,m), 7.43(1H,s), 7.61(1H,d,J=8.0Hz).

ESI-Mass ; 353(MH+).

Example 392: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1-hydroxyethyl)indole oxalate

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-formylindoline (0.15 g) obtained in Example 130 was dissolved in tetrahydrofuran (5 ml) and stirred under ice cooling. To the resultant solution was added a 1.0 M solution (0.5 ml) of methylmagnesium bromide in ether and the mixture was stirred for 30 min. Then a saturated aqueous solution of ammonium

chloride, water and ethyl acetate were added to the reaction solution. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. After evaporating the solvent under reduced pressure, a free title compound (0.13 g) was obtained as a pale brown viscous oil, which was then converted into an oxalate in a conventional manner.

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 1.38(3H,d,J=6.4Hz), 2.10(2H,br-d), 2.24-2.33(2H,m), 2.98-3.02(2H,m), 3.06(2H,br-t), 3.16-3.20(2H,m), 3.56(2H,br-d), 4.63-4.70(1H,m), 6.44(1H,d,J=3.2Hz), 7.03(1H,d,J=8.4Hz), 7.18(2H,br-t), 7.34-7.37(2H,m), 7.41(1H,d,J=3.2Hz), 7.47(1H,d,J=8.4Hz), 7.53(1H,s).

ESI-Mass ; 367(MH+).

Example 393: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-ureidomethylindole

1,1-Carbonyldiimidazole (0.16 g) and imidazole (0.13 g) were added to tetrahydrofuran (5 ml) and the resultant mixture was stirred under nitrogen atmosphere under ice cooling. Next, 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminomethylindoline (0.33 g) obtained in Example 132 dissolved in tetrahydrofuran (3 ml) was added dropwise thereinto. After stirring for 15 min, a saturated solution (2 ml) of ammonia in ethanol was further added thereto and the resultant mixture was

stirred under ice cooling for 10 min and then at room temperature overnight. Next, water and ethyl acetate were added to the reaction solution. The organic layer was separated, washed with brine and dried over magnesium sulfate. After evaporating the solvent under reduced pressure, the residue was purified by silica gel column chromatography (chloroform/methanol system) to give the title compound as colorless crystals. Then these crystals were recrystallized from chloroform/ethyl acetate/n-hexane to give the title compound (0.07 g) as colorless needles.

m.p.: 171.9 - 172.8°C.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.02-2.10(4H,m), 2.20-2.26(2H,m), 2.60-2.64(2H,m), 2.78-2.82(2H,m), 3.12(2H,br-d), 4.16-4.24(1H,m), 4.37(2H,d,J=5.4Hz), 4.58(2H,s), 5.34(1H,t,J=5.4Hz), 6.47(1H,d,J=3.2Hz), 6.96-7.00(3H,m), 7.15-7.18(2H,m), 7.21(1H,d,J=3.2Hz), 7.29(1H,s), 7.54(1H,d,J=8.0Hz).

ESI-Mass ; 395(MH+).

Example 394: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(3-methylureido)methylindole

1-[1-(4-Fluorophenethyl)piperidin-4-yl]-6-aminomethylindoline (0.17 g) obtained in Example 132 was dissolved in tetrahydrofuran (5 ml) and the resultant solution was stirred under nitrogen atmosphere. After adding methyl

isothiocyanate (40.4 ml), the mixture was stirred for additional 50 min. Then additional methyl isothiocyanate (40.4 ml) was added thereto and the mixture was further stirred for 30 min. After evaporating the solvent under reduced pressure, the residue was purified by NH-silica gel column chromatography (ethyl acetate/n-hexane system) to give the title compound (0.14 g) as a pink amorphous substance.

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 2.07-2.12(4H,m), 2.26-2.33(2H,m), 2.64-2.68(2H,m), 2.81-2.85(2H,m), 2.96(3H,br-d), 3.17(2H,br-d), 4.22-4.30(1H,m), 4.71(2H,br-s), 5.87(1H,br-s), 6.09(1H,br-s), 6.52(1H,d,J=3.2Hz), 6.99(2H,br-t), 7.05(1H,d,J=8.0Hz), 7.17-7.20(2H,m), 7.27(1H,d,J=3.2Hz), 7.37(1H,s), 7.61(1H,d,J=8.0Hz).

ESI-Mass ; 425(MH+).

Example 395: Synthesis of 3,3-dimethyl-1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-acetamidoindoline

395-1) 3,3-Dimethyl-1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminomethylindoline

Into a solution of 3,3-dimethyl-1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-bromoindoline (1.50 g) obtained in Example 293 in tetrahydrofuran (50 ml) was added dropwise at - 78°C a 1.6 M solution (3 ml) of n-butyllithium in hexane. After 10 min, dimethylformamide (0.3 ml) was added thereto and the resultant mixture was warmed to room temperature. Then a

saturated aqueous solution of ammonium chloride (20 ml) and ethyl acetate (100 ml) were added thereto and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. From the resulting residue, 3,3-dimethyl-1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-formylindoline (0.68 g) was separated by silica gel column chromatography (ethyl acetate). Then it was suspended in a solution of hydroxylammonium chloride (0.15 g) and anhydrous sodium acetate (0.18 g) in ethanol (20 ml) and stirred at room temperature for 2 hr. The reaction mixtures were concentrated under reduced pressure and diluted with ethyl acetate (50 ml), a 2 N aqueous solution of sodium hydroxide (10 ml) and water (10 ml). The organic layer was separated, washed with brine and dried over magnesium sulfate. After evaporating the solvent, the obtained 3,3-dimethyl-1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-hydroxyiminomethylindoline (0.55 g) was dissolved in tetrahydrofuran (5 ml). The resultant solution was added dropwise under ice cooling and stirring into a suspension of lithium aluminum hydride (0.07 g) in tetrahydrofuran (50 ml) and then heated under reflux for 3 hr. Under ice water cooling, water (0.07 ml), a 5 N aqueous solution (0.21 ml) of sodium hydroxide and further water (0.07 ml) were carefully added dropwise into the reaction mixtures in this order followed by

vigorous stirring. The resulting precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by NH-silica gel column chromatography (ethyl acetate/methanol system) to give the title compound (0.23 g) as a brown amorphous substance (total yield: 17.4 %).

¹H-NMR(400MHz,CDCl₃) ; δ(ppm) 1.24(6H,s), 1.78-2.10(4H,m), 2.38-2.51(2H,m), 2.72-2.83(2H,m), 2.89-2.98(2H,m), 3.17(2H,s), 3.20-3.35(2H,m), 3.42-3.55(1H,m), 6.61(1H,s), 6.88(1H,d,J=8.0Hz), 6.94-7.01(3H,m), 7.14-7.20(2H,m).

395)-2 3,3-Dimethyl-1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindoline

Under ice cooling, acetyl chloride (0.05 ml) was added dropwise into a solution of 3,3-dimethyl-1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminomethylindoline (0.22 g) obtained above and triethylamine (0.5 ml) in tetrahydrofuran (10 ml) and the resultant mixture was stirred at room temperature for 1 hr. Then a 1 N aqueous solution (5 ml) of sodium hydroxide and water (10 ml) were added to the reaction mixture, which was extracted with ethyl acetate, washed with brine and dried over magnesium sulfate. After evaporating the solvent, the residue was purified by silica gel column chromatography (chloroform/methanol system) and crystallized from ethyl acetate/hexane to give the title compound (0.18 g) as a yellowish white powder (yield: 73.7 %).

m.p.: 131 - 133°C.

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 1.21(6H,s), 1.83(3H,s),
1.80-2.06(4H,m), 2.98-3.20(4H,m), 3.07(2H,s), 3.21-
3.42(2H,m), 3.58-3.68(1H,m), 4.14(2H,d,J=6Hz), 6.41(1H,s),
6.50(1H,br-d), 6.94(1H,br-d), 7.14-7.22(2H,m), 7.28-
7.38(2H,m), 8.17-8.21(1H,m).

ESI-Mass ; 428(MH+).

Example 396: Synthesis of 2,2-dimethyl-1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methoxyindoline
396-1) N-(1-Acetylpiperidin-4-yl)-3-methoxyaniline

Under ice cooling, sodium triacetoxyborohydride (12.0 g) was added to a liquid mixture of m-anisidine (4.40 g), 1-acetylpiperidin-4-one (5.0 g) and acetic acid (8 ml) in dichloroethane (80 ml). Then the reaction mixtures were stirred at room temperature overnight. The reaction mixtures were diluted with ethyl acetate (200 ml) and a 5 N aqueous solution (35 ml) of sodium hydroxide was added thereto. The organic layer was separated, washed successively with water and brine and dried over magnesium sulfate. After evaporating the solvent under reduced pressure, the residue was purified by silica gel column chromatography (ethyl acetate/hexane system) to give the title compound (7.80 g) as a brown oil (yield: 87.9 %).

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 1.30-1.45(2H,m), 2.06-

2.18(2H,m), 2.11(3H,s), 2.76-2.85(1H,m), 3.13-3.22(1H,m),
3.43-3.51(1H,m), 3.78(3H,s), 3.76-3.93(1H,m), 4.46-
4.53(1H,m), 6.24(1H,br-s), 6.28-6.36(2H,m),
7.11(1H,t,J=8.0Hz).

396-2) N-(1-Acetylpiperidin-4-yl)-N-(2-methyl-2-propen-1-yl)-3-methoxyaniline

A mixture of N-(1-acetylpiperidin-4-yl)-3-methoxyaniline (2.0 g), 3-chloro-2-methylpropene (10 ml) and potassium carbonate (5.0 g) in dimethylformamide (50 ml) was reacted at 80°C for 6 hr. Then the reaction mixtures were concentrated under reduced pressure and partitioned between ethyl acetate and water. The ethyl acetate layer was washed successively with water and brine and dried over magnesium sulfate. After evaporating the solvent under reduced pressure, the residue was purified by silica gel column chromatography (ethyl acetate/hexane system) to give the title compound (1.55 g) as a yellow oil (yield: 63.6 %).

¹H-NMR(400MHz,CDCl₃) ; δ (ppm) 1.46-1.60(2H,m), 1.73(3H,s),
1.86-1.98(2H,m), 2.11(3H,s), 2.58(1H,dt,J=8.8,2.4Hz),
3.14(1H,dt,J=8.8,2.4Hz), 3.59(2H,s), 3.77(3H,s), 3.80-
3.94(2H,m), 4.73-4.81(1H,s), 4.87(2H,d,J=9.2Hz), 6.22-
6.37(3H,m), 7.12(1H,t,J=8.0Hz).

396-3) 2,2-Dimethyl-1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methoxyindoline

Under nitrogen atmosphere, N-(1-acetylpiperidin-4-yl)-N-(2-methyl-2-propen-1-yl)-3-methoxyaniline (1.50 g) was heated under reflux in the presence of zinc chloride (2.0 g) in xylene (30 ml) for 4 hr. After cooling the reaction mixtures, a 5 N aqueous solution (20 ml) of sodium hydroxide and ethyl acetate (100 ml) were added thereto and the resultant mixture was stirred for 30 min. The ethyl acetate layer was separated, washed successively with water and brine and dried over magnesium sulfate. After evaporating the solvent, the residue was dissolved in ethanol (30 ml). Then a 5 N aqueous solution (10 ml) of sodium hydroxide was added thereto and the mixture was heated under reflux for 2.5 hr. After concentrating the mixture, the residue was partitioned between ethyl acetate and water followed by extraction with ethyl acetate. The ethyl acetate layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane system) to give a yellow oily mixture (0.91 g) containing 2,2-dimethyl-1-(piperidin-4-yl)-6-methoxyindoline.

This mixture was reacted with 4-fluorophenethyl bromide (0.8 g) in N,N-dimethylformamide (20 ml) in the presence of potassium carbonate (1.5 g) at 70°C for 6 hr. Then the reaction mixtures were concentrated under reduced pressure and

the residue was partitioned between water and ethyl acetate followed by extraction with ethyl acetate. The ethyl acetate layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by high performance liquid chromatography (ODS column, acetonitrile/water/70 % perchloric acid system). After concentrating the solvent, the residue was basified, extracted with ethyl acetate, washed with water, dried and concentrated to give the title compound (0.31 g) as a pale yellow oil.

Next, this product was converted into an oxalate in a conventional manner to give a pale greenish blue powder.

Oxalate:

m.p.: 228°C (decomp.).

¹H-NMR(400MHz,DMSO-d₆) ; δ (ppm) 1.22(6H,s), 1.58-1.69(2H,m), 2.50-2.75(4H,m), 2.94-3.11(4H,m), 3.15-3.25(2H,m), 3.36-3.61(3H,m), 3.66(3H,s), 6.01(1H,d,J=8Hz), 6.22(1H,s), 6.82(1H,d,J=8Hz), 7.14-7.24(2H,m), 7.30-7.38(2H,m).

ESI-Mass ; 383(MH+).

Example 397: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(3-methylureido)methylindole

Under ice cooling, methyl isocyanate (0.02 g) was added dropwise into a solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminomethylindoline (0.09

g) obtained in Example 132 in ethyl acetate (10 ml) and the resultant mixture was stirred at room temperature for 1 hr. The resulting precipitate was collected by filtration, washed with ether/hexane and dried to give the title compound (0.07 g) as a white powder (yield: 67 %).

m.p.: 192°C (decomp.).

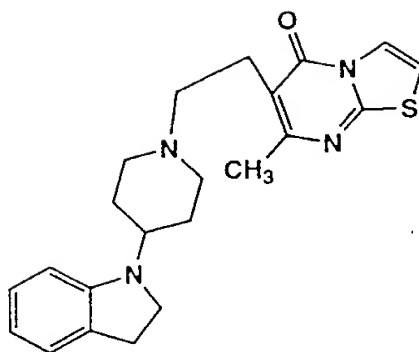
¹H-NMR(400MHz,DMSO-d₆) ; δ(ppm) 1.88-2.04(4H,m), 2.19-2.27(2H,m), 2.54-2.61(2H,m), 2.57(3H,d,J=4.4Hz), 2.74-2.80(2H,m), 3.09(2H,br-d), 4.25-4.34(1H,m), 4.28(2H,d,J=6.0Hz), 5.73-5.78(1H,m), 6.26-6.32(1H,m), 6.40(1H,d,J=3.2Hz), 6.94(1H,d,J=8.0Hz), 7.08-7.14(2H,m), 7.27-7.32(2H,m), 7.39(1H,s), 7.44-7.48(2H,m).

ESI-Mass ; 409(MH+).

The Chemical formula of the compounds of Ex. 294 to 397 are cited below.

Referential Example 1: Synthesis of 1-{1-[2-(5-oxo-7-methyl-5H-pyrimidino[2,1-b][1,3]thiazol-6-yl)ethyl]piperidin-4-yl}indoline

[Co. No. 5 disclosed in WO96/23784]



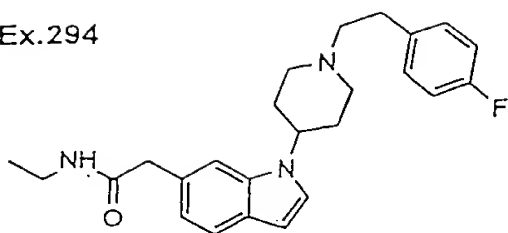
1-[1-(2-Aminoethyl)piperazin-4-yl]indoline (192 mg) was dissolved in DMF (5 ml) and then 7-methyl-6-(2-chloroethyl)-5H-pyrimidino[2,1-b][1,3]thiazol-5-one (239 mg) and triethylamine (0.159 ml) were added thereto. Next, the resultant mixture was stirred at 80°C for 11 hr and then at 100°C for 8 hr. After adding water, the reaction solution was extracted with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. After evaporating the solvent, the resulting residue was purified by silica gel column chromatography (methanol/methylene chloride system) to give the title compound (46 mg) as an oil.

¹H-NMR (400 MHz, CDCl₃):

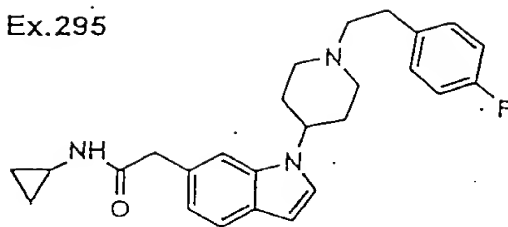
δ(ppm) 1.60-1.89(6H, m), 2.15-2.24(2H, m), 2.45(3H, s), 2.51-2.58(2H, m), 2.82-2.88(2H, m), 2.94(2H, t, J=8.2Hz), 3.14-3.22(2H, m), 3.39(2H, t, J=8.2Hz), 3.36-3.44(1H, m), 6.41(1H, d, J=7.6Hz), 6.60(1H, t, J=7.6Hz), 6.92(1H, d, J=4.8Hz), 7.01-7.07(2H, m), 7.91(1H, d, J=4.8Hz).

FAB-Mass: 395(MH⁺).

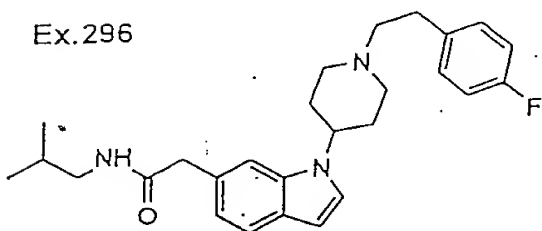
Ex.294



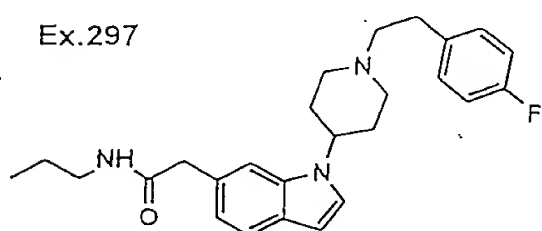
Ex.295



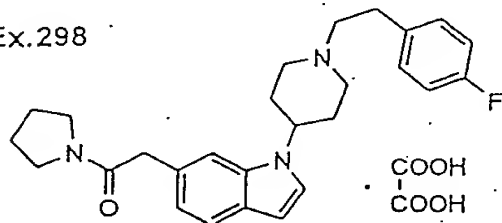
Ex.296



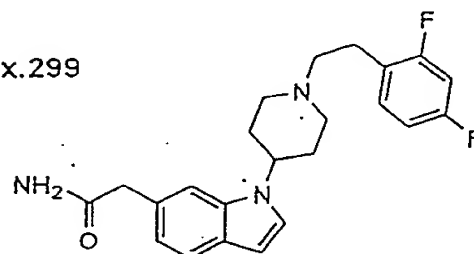
Ex.297



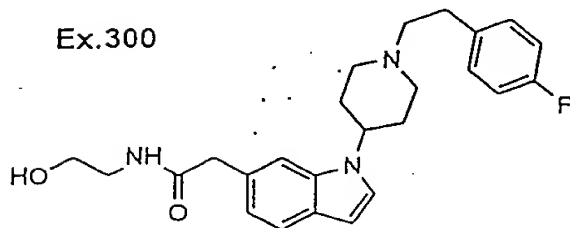
Ex.298



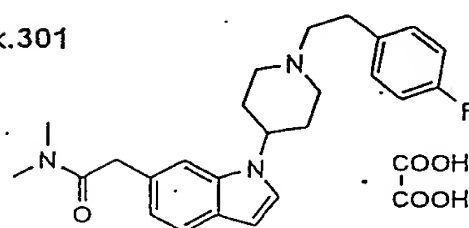
Ex.299



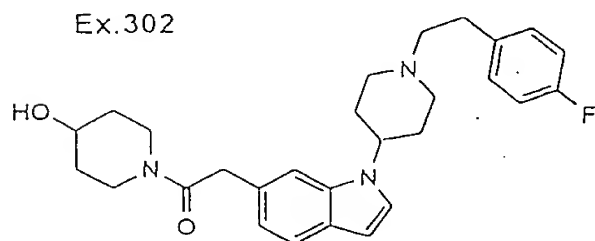
Ex.300



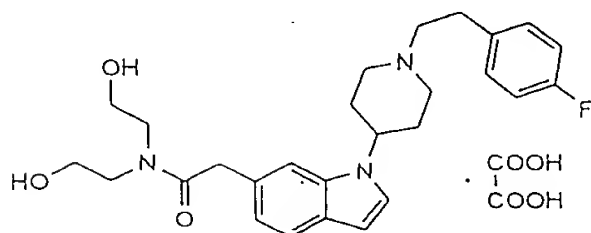
Ex.301



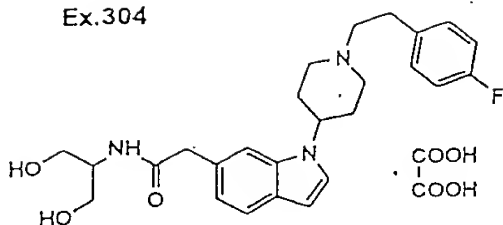
Ex.302



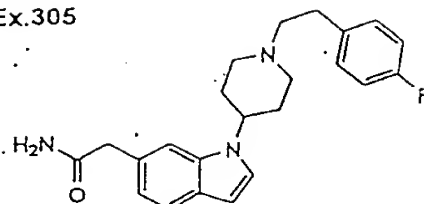
Ex.303



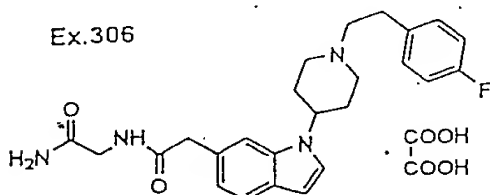
Ex.304



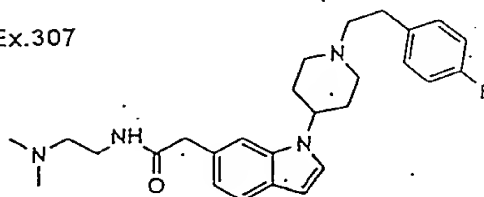
Ex.305



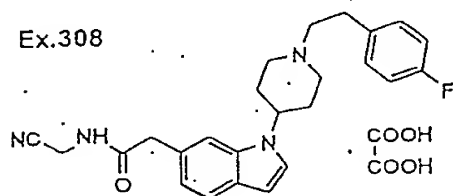
Ex.306



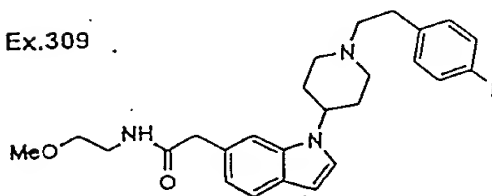
Ex.307



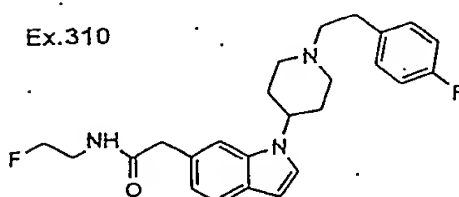
Ex.308



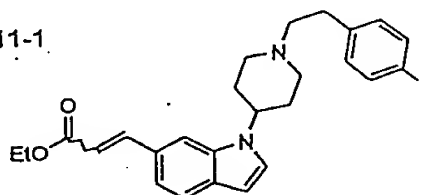
Ex.309



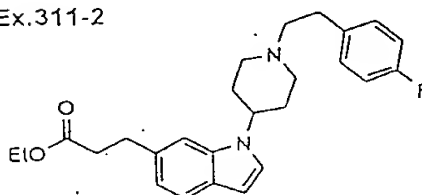
Ex.310



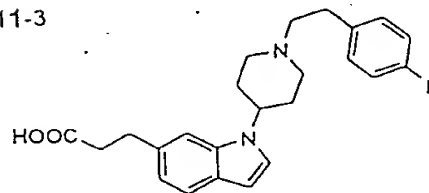
Ex.311-1



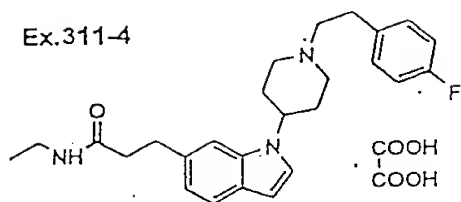
Ex.311-2



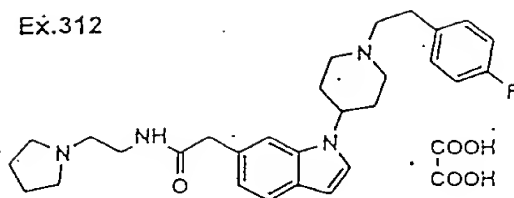
Ex.311-3



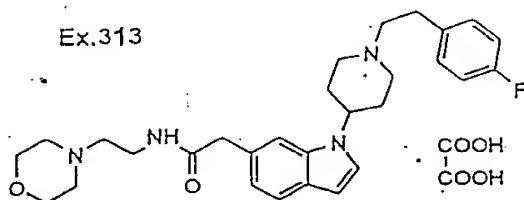
Ex.311-4



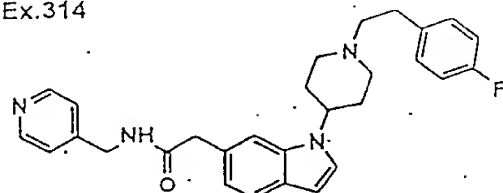
Ex.312



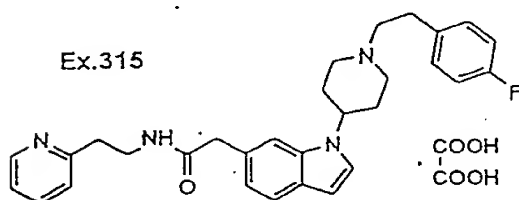
Ex.313



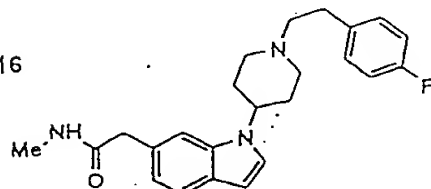
Ex.314



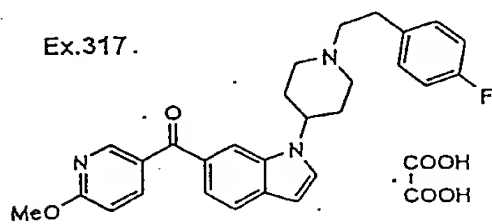
Ex.315



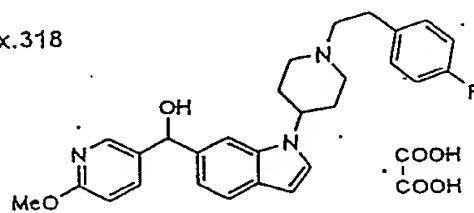
Ex.316



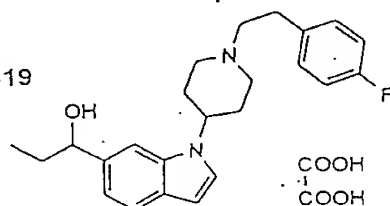
Ex.317.



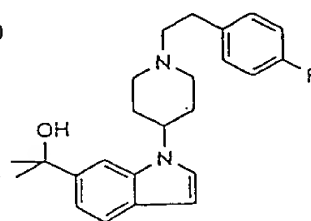
Ex.318



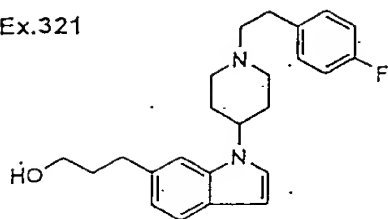
Ex.319



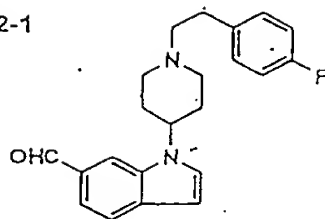
Ex.320



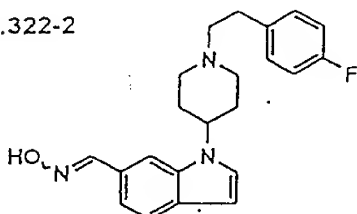
Ex.321



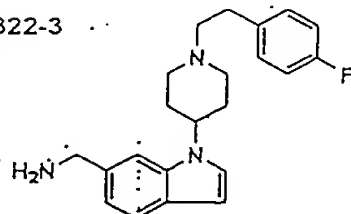
Ex.322-1



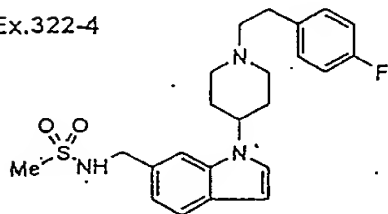
Ex.322-2



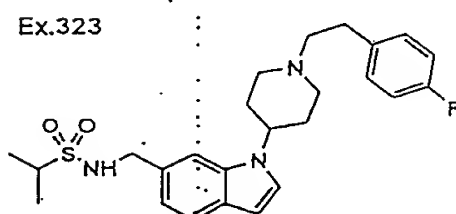
Ex.322-3



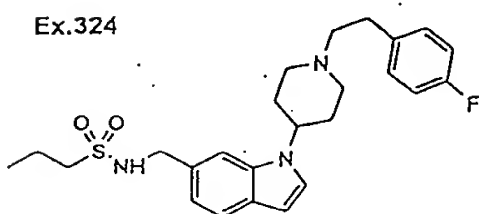
Ex.322-4



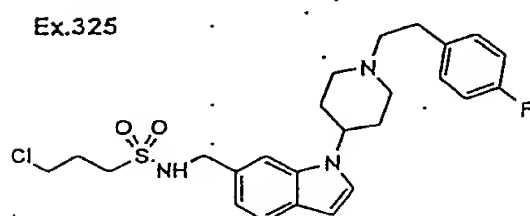
Ex.323



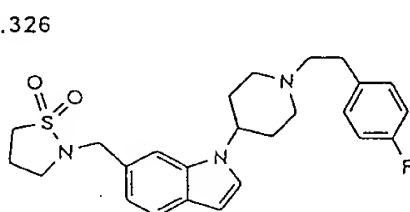
Ex.324



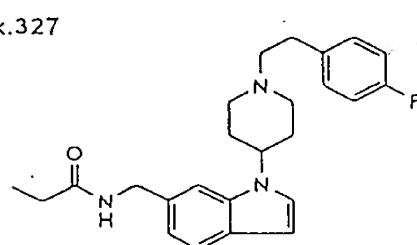
Ex.325



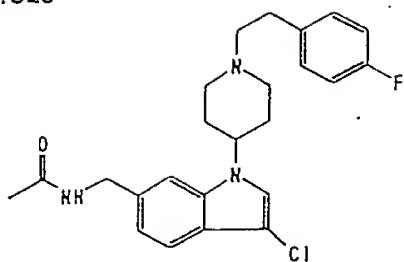
Ex.326



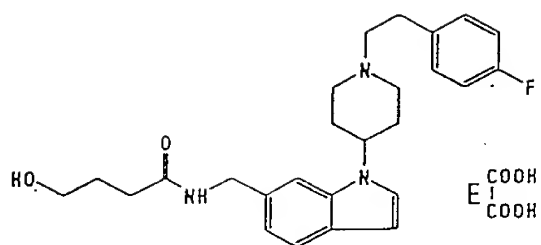
Ex.327



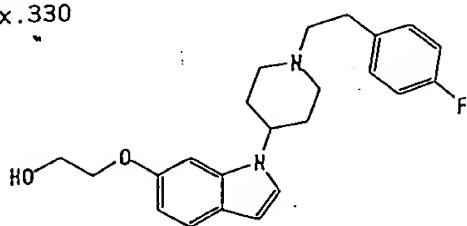
Ex. 328



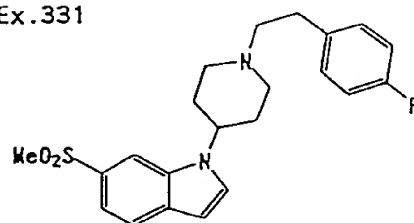
Ex. 329



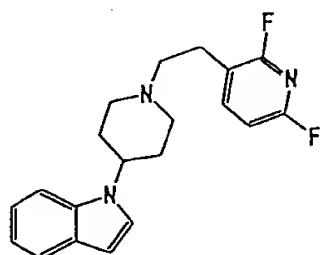
Ex. 330



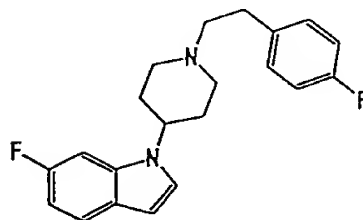
Ex. 331



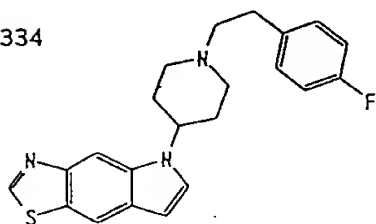
Ex. 332



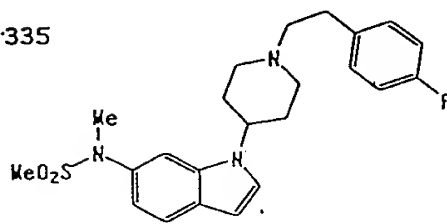
Ex. 333



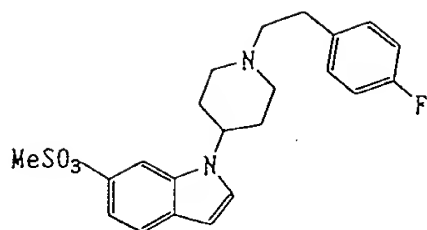
Ex. 334



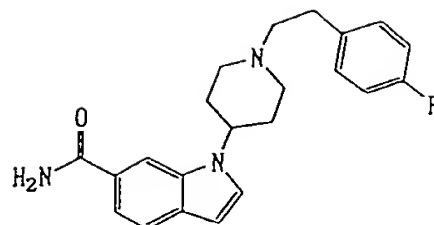
Ex. 335



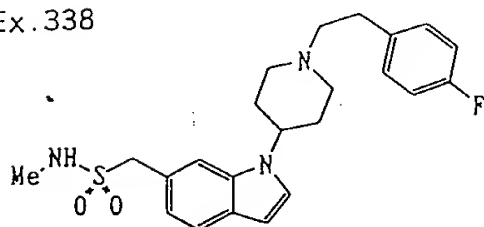
Ex. 336



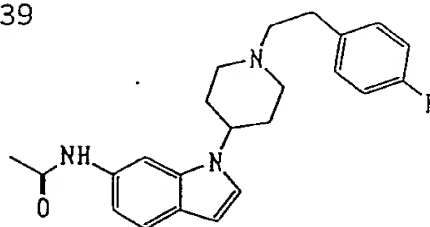
Ex. 337



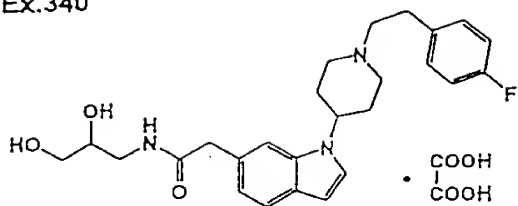
Ex. 338



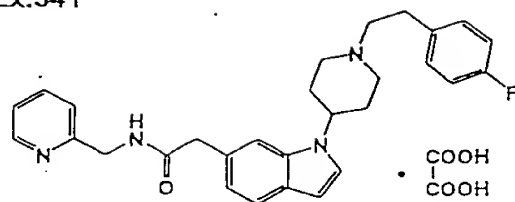
Ex. 339



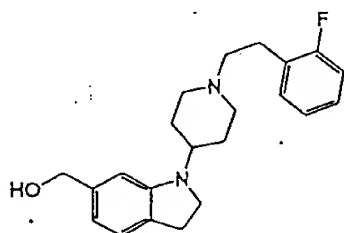
Ex.340



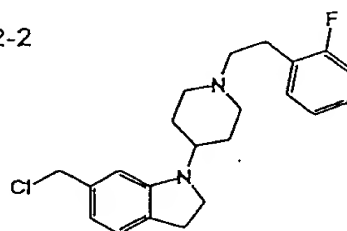
Ex.341



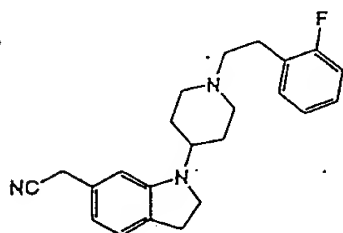
Ex.342-1



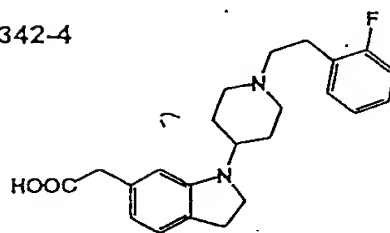
Ex.342-2



Ex.342-3



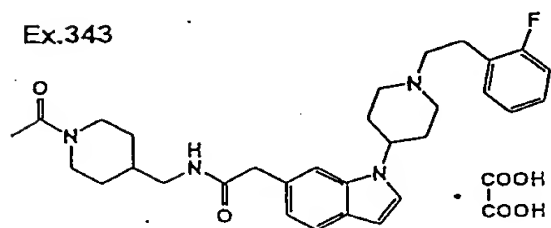
Ex.342-4



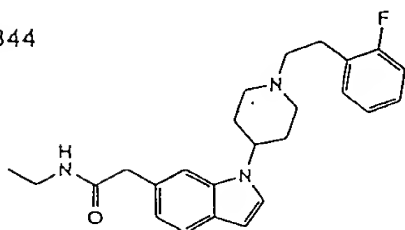
Ex.342-5



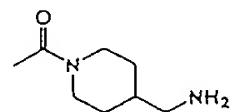
Ex.343



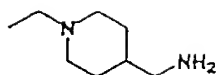
Ex.344



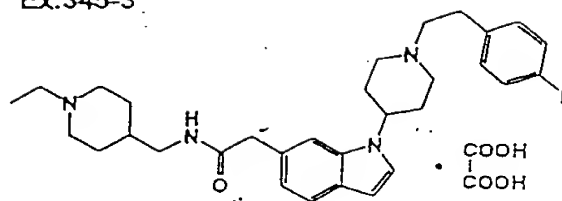
Ex.345-1



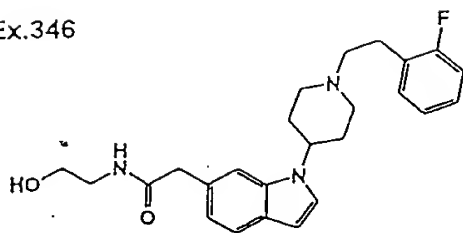
Ex.345-2



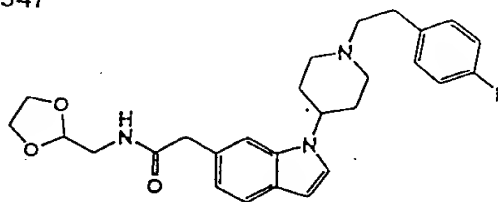
Ex.345-3



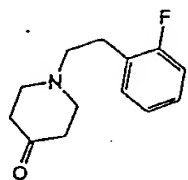
Ex.346



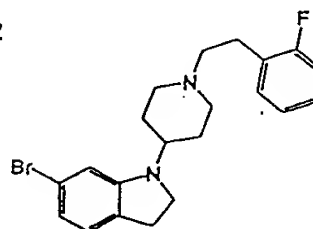
Ex.347



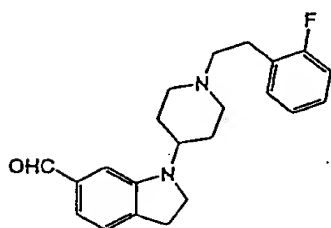
Ex.348-1



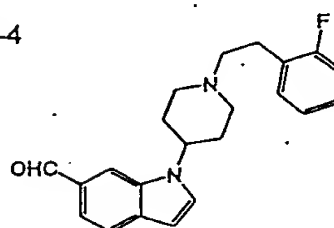
Ex.348-2



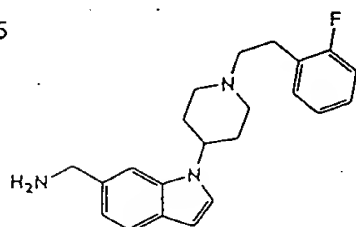
Ex.348-3



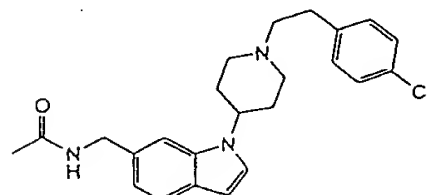
Ex.348-4



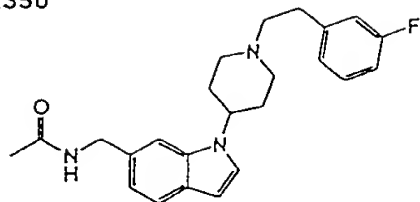
Ex.348-5



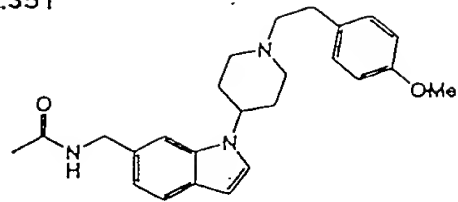
Ex.349



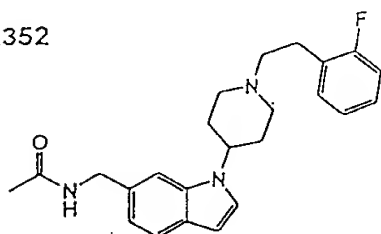
Ex.350



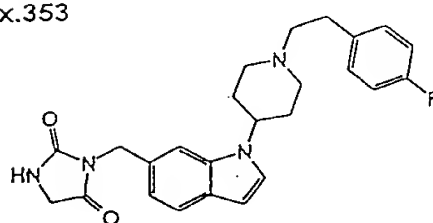
Ex.351



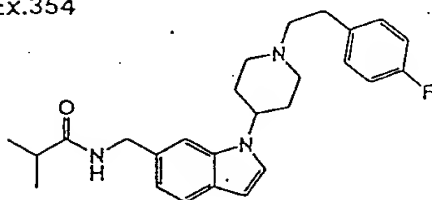
Ex.352



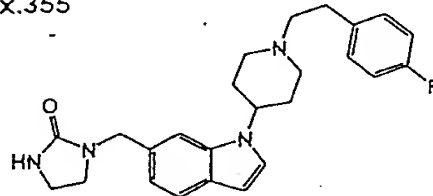
Ex.353



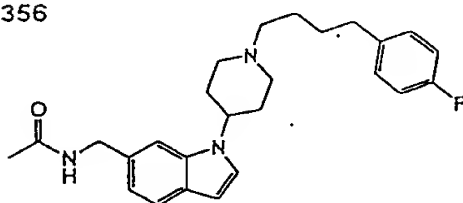
Ex.354



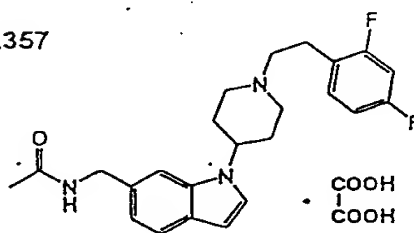
Ex.355



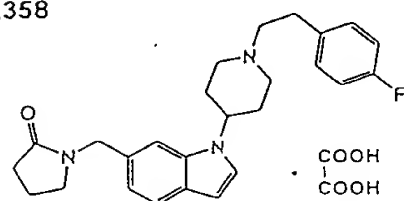
Ex.356



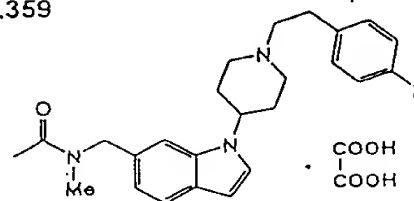
Ex.357



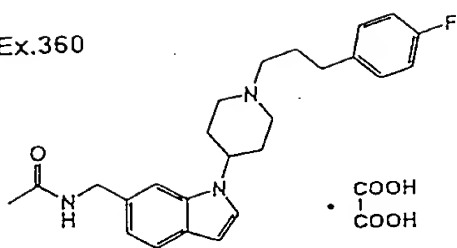
Ex.358



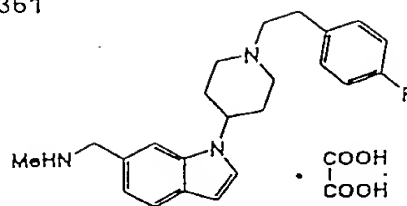
Ex.359



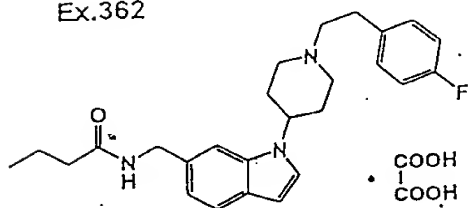
Ex.360



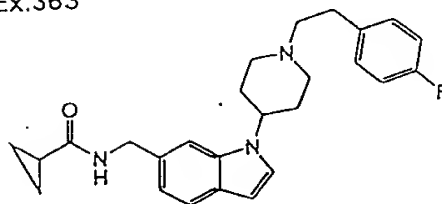
Ex.361



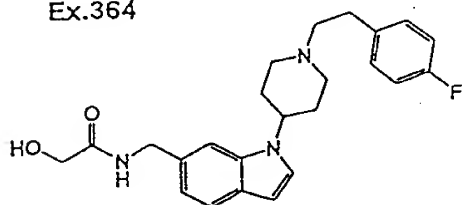
Ex.362



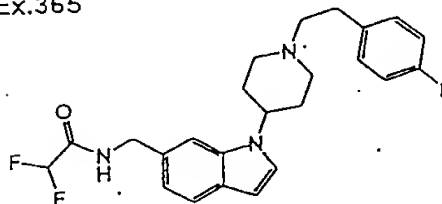
Ex.363



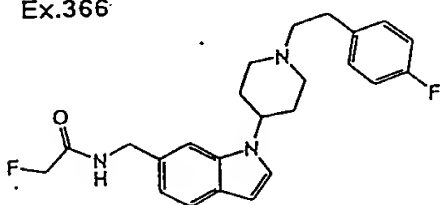
Ex.364



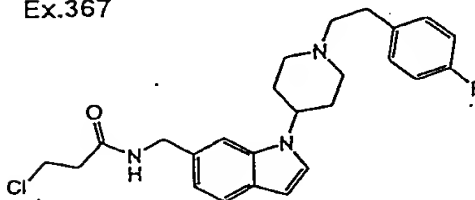
Ex.365



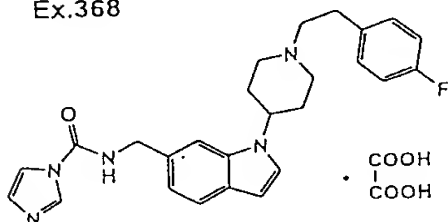
Ex.366



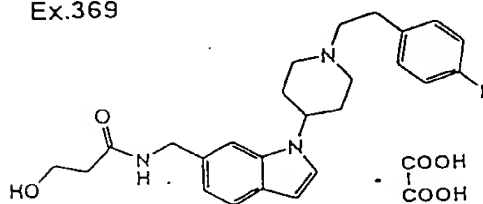
Ex.367



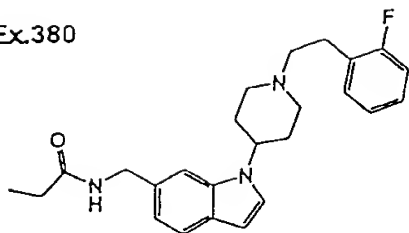
Ex.368



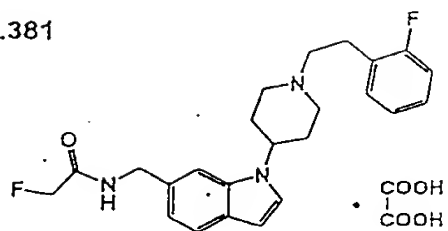
Ex.369



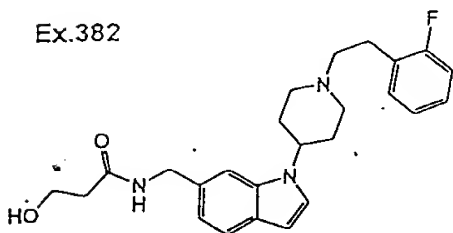
Ex.380



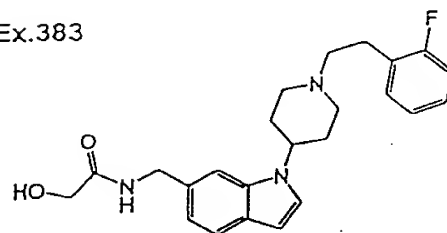
Ex.381



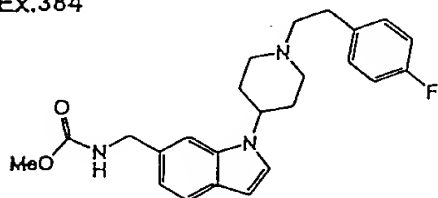
Ex.382



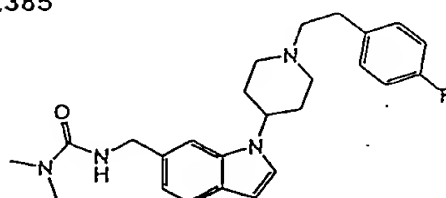
Ex.383



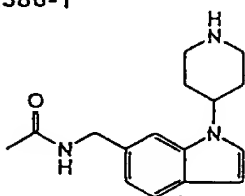
Ex.384



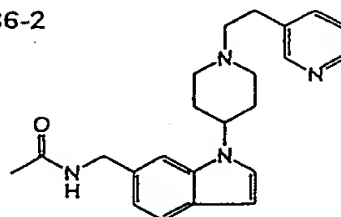
Ex.385



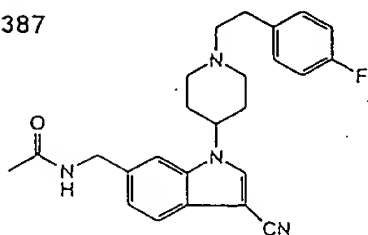
Ex.386-1



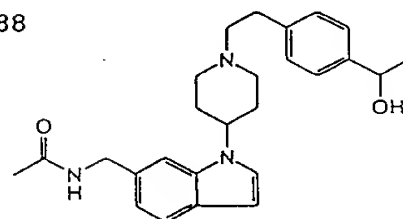
Ex.386-2



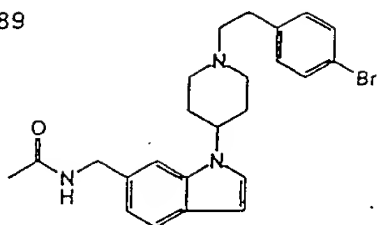
Ex.387



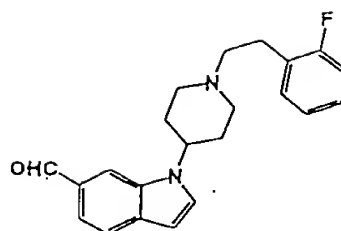
Ex.388



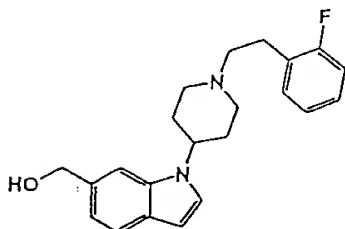
Ex.389



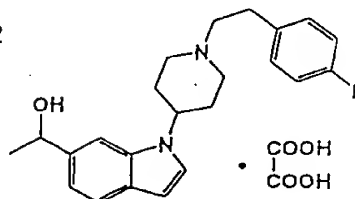
Ex.390



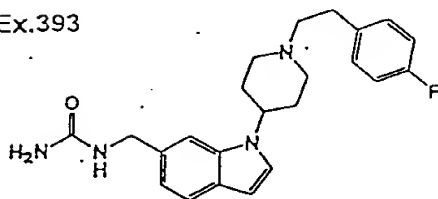
Ex.391



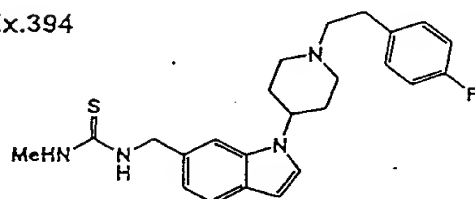
Ex.392



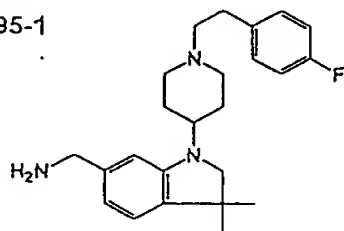
Ex.393



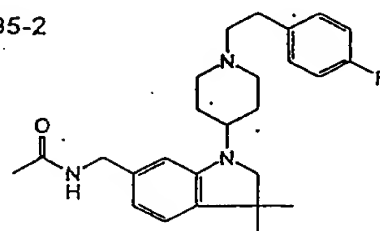
Ex.394



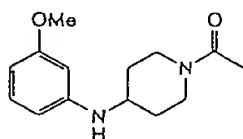
Ex.395-1



Ex.395-2



Ex.396-1



Ex.396-2

